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CHRONIC THYROIDITIS AND PRIMARY THYROTOXICOSIS (EXOPHTHALMIC GOITER)

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TRANSLATED BY PERIHAN CAMBEL, M.D.*

At the present time the different clinical manifestations produced by various pathologic changes in the thyroid gland cannot be considered as well defined, standardized diseases the classification of which is beyond all criticism. Observations recorded in the modern literature on the various kinds of inflammation and dysfunction of this gland are varied and do not always necessarily correspond clinically and anatomically. These diverse observations oppose at times the attempt to classify the pathologic conditions of the thyroid gland. So it is the purpose of this paper to present a peculiar case of chronic thyroiditis which does not seem to fit the generally known description.

HISTORICAL REVIEW

In 1896 Riedel [1] reported a disease which until then had been unknown, a new form of "inflammatory condition in which fibrosis eventually dominates the picture" (Joll [2]). The patient, a man aged 40, had shown the symptoms of life-threatening dysphonia and asphyxia, hoarseness and a hard, immovable, painless, enlarged thyroid gland. Riedel's clinical diagnosis had been cancer. Extensive adhesions of the gland to the surrounding parts obliged him to abandon resection and resort to excision of a small portion. Microscopic examination revealed chronic inflammation. Riedel called the new condition "iron-hard goitre." His observations on a second case, a year later, induced him to define closely this new term. In 1897 he presented a third case. According to Joll,[2] the well known English authority on diseases of the thyroid, Bowlby reported a case (1884) in which a condition identical with Riedel's disease was observed at autopsy; but "Riedel's description of the condition, in 1896, led to its recognition as a clinical and pathological entity."

Cordua was the second to demonstrate the same histologic structure in a thyroid gland, on which he could not perform resection because of too extensive adhesions. In 1898 Tailhefer, of Toulouse, operated in a case in which the clinical manifestations were similar to those in Riedel's cases; he examined microscopically the excised thyroid tissue, corresponded with Riedel about the case and published a report of it. It was the first case of Riedel's disease observed in France. New cases were added to the world literature, and new authors compared histologic and clinical observations; terms like *inflammation chronique primitive cancériforme* (Tailhefer), *thyroidité ligneuse* (Delore and Alamartine) and benign granuloma of the thyroid (Ewing [3]) were introduced.

Riedel concluded that chronic thyroiditis was the result of an infection with an unknown agent, which spread by the hematogenous or lymphogenous route to the thyroid. Tailhefer expressed the opinion that the agent was Staphylococcus albus. Evidence of tuberculosis or syphilis could not be adduced. In spite of the nonspecific structure of the inflammatory lesions, some authors did not dismiss the possibility of tuberculosis as an etiologic factor, stating that this disease may produce nonspecific inflammatory lesions in glandular organs (Wegelin [4]). Reist [5] and von Werdt,[6] stated the belief that iodine was a causative agent. The inflammatory reaction, however, observed in iodine-treated exophthalmic goiters (colloid stage) does not

* From the Second Department of Surgery, Istanbul University.

1. Riedel, 1896, cited by Reist.[5]

2. Joll, C. A.: Diseases of the Thyroid Gland, London, William Heinemann, Ltd., 1932.

3. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1934.

4. Wegelin, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926.

5. Reist, A.: Frankfurt. Ztschr. f. Path. **28**:141, 1922.

6. von Werdt, F.: Frankfurt. Ztschr. f. Path. **7**:401, 1911; cited by Reist.[5]

correspond to the morphologic changes associated with Riedel's disease. The histologic changes observed by Orywall [7] in the thyroids of iodine-fed mice also cannot be compared with the structure of Reidel's goiter; in the former there were simply slight alterations in the epithelial cells and the colloidal content and a slight increase of connective tissue.

The results of the partly comparative studies of acute, subacute and chronic inflammatory processes of the thyroid prove that Riedel's goiter is a chronic thyroiditis, with a typical clinical course and a typical histologic structure. Microscopically, an increase of the connective tissue, reaching the most extreme degree, and a dense interlobar and intralobar inflammatory infiltration with lymphocytes, plasma cells and mononuclear cells are observed. Lymph follicles, which, according to Joll, are characteristic only of lymphadenoid goiter, may be encountered. The glandular vesicles are greatly affected and damaged by the inflammatory process. On the whole, Riedel's goiter was differentiated clinically and histologically from the acute and subacute inflammations, from lymphadenoid goiter and Simmonds' atrophy. Wegelin, de Quervain, Reist, Simmonds, Hashimoto and Joll established the modern differential diagnosis of the various inflammatory conditions of the thyroid. Weyeneth [8] contributed the newest and most comprehensive publications in this field, including reports of his own cases and a critical review of the world literature.

Opposing the upholders of these concepts are the so-called unitarians (Ewing, Vaux and others), who do not differentiate Riedel's goiter (chronic thyroiditis) and Hashimoto's struma (struma lymphomatosa). On the other hand, Graham, MacCullagh, Joll, Polowe [9] and others stated the belief that lymphadenoid goiter is observed only in certain countries, such as Japan, India, England and North America. Recently 8 new cases were added by Weyeneth and Chaval, all of which came from the Swiss Canton of Geneva.

Chronic thyroiditis per se is rare in practically all countries. In 1941 de Quervain [10] expressed the opinion that the condition is still unknown to some pathologists on the European continent. Even today cases may be referred to the surgeon in which the clinical diagnosis of cancer of the thyroid has been made. In other cases reliable pathologists may mistake the polymorphic and proliferative changes in the epithelium for signs of malignancy (McClintock and Wright [11]). As everywhere, chronic thyroiditis is rare in Turkey. Cambel [12] reported a case of pemphigus with chronic thyroiditis observed at autopsy. No other cases have been reported in Turkey as far as I know.

Fig. 1.—Patient (*A*) before and (*B*) after thyroidectomy.

REPORT OF A CASE

F. E., a merchant aged 56, born in Odemis (Anatolia), had lived in Istanbul, Edirne and various other places in Turkey. The patient was admitted to the hospital on Oct. 5, 1942 for swelling of the neck, exophthalmos, hoarseness, dyspnea, loss of weight and sleeplessness (fig. 1 *A*). The first symptoms, which had appeared one or two years before, consisted of severe diarrhea, continuous nervousness, loss of weight, sleeplessness and tremor of the hands and legs. The patient had weighed 72 Kg., but his weight was reduced to 44 Kg. After treatment for rheumatism and heart disease, he gained 16 Kg. In 1942 the symptoms reappeared. The diagnosis made in the military Marine Hospital and in the university clinic for therapeutics (Prof. Dr. Akil Muhtar Ozden) was exophthalmic goiter. In the clinic the basal metabolic rate was

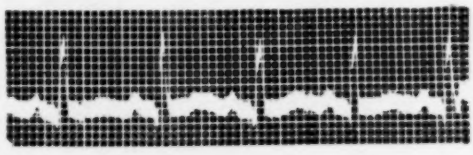

Fig. 2.—Electrocardiogram taken before thyroidectomy.

+76 at the first and +87 at the second examination. The electrocardiogram (fig. 2) showed sinus tachycardia (typical of exophthalmic goiter). A disturbing and increasing prurigo caused the patient to scratch himself with a knife and finally to discontinue treatment.

Examination.—A scarcely movable, hard, diffusely enlarged thyroid gland was found on palpation. The

7. Orywall, W.: Virchows Arch. f. path. Anat. **287**:348, 1932.

8. Weyeneth, R.: (*a*) Arch. f. klin. Chir. **201**:457, 1941; (*b*) Rev. méd. de la Suisse Rom. **63**:681, 1943.

9. Polowe, D.: Struma Lymphomatosa (Hashimoto) Associated with Hyperthyroidism: Report of Case with Clinical and Histopathologic Study, Arch. Surg. **29**:768 (Nov.) 1934.

10. de Quervain, F.: Die Struma maligna, Stuttgart, Ferdinand Enke, 1941.

11. McClintock, J. C., and Wright, A. W.: Ann. Surg. **106**:32, 1937.

12. Cambel, P.: Dermatologica **3**:127, 1943.

enlargement was more pronounced on the right side of the neck. Exophthalmos and positive Stellwag and Möbius signs were noted. The pulse rate was 130 and the basal metabolic rate + 80. The patient was 1.67 meters tall and weighed 53 Kg. A roentgenogram showed dilatation of the left side of the heart. Chemical examination of the urine and the blood cell count revealed nothing. The diarrhea disappeared, but the sleeplessness continued.

The clinical diagnosis was cancer of the thyroid.

Operation.—Operation was performed on Oct. 10, 1942, with the area under local anesthesia induced with a 0.5 per cent solution of procaine hydrochloride (Prof. Dr. Kazim Gürkan). In spite of extensive adhesions of the thyroid to the joining tissues, an almost total thyroidectomy was performed.

Pathologic Report.—The report of the pathologist, Dr. Perihan Cambel, was as follows:

Gross Examination: The surgical specimen consisted of two well encapsulated lobes of the thyroid, weighing 40 Gm. and showing the areas of resection. The capsule was conspicuous but not noticeably thickened. The cut surfaces of the thyroid were light brownish and homogeneous. The thyroid tissue was divided by white connective tissue bands into small lobules.

Microscopic Examination: The lobules of the thyroid gland were separated from one another by thickened, collagenous connective tissue bands and were

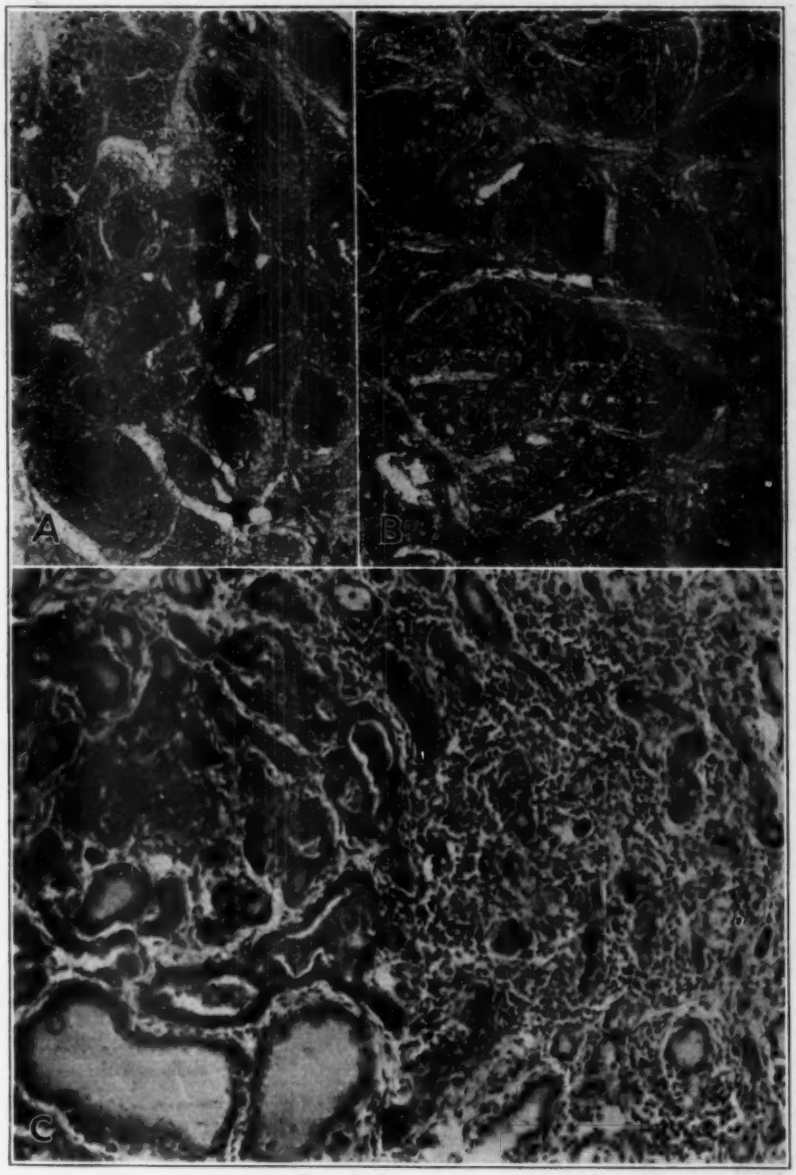

Fig. 3.—Photomicrographs: *A*, chronic inflammatory infiltration, with the formation of lymph follicles partly replacing thyroid tissue. *B*, slighter inflammatory infiltration, showing acini with decreased colloid content. *C*, interlobar inflammatory infiltration, intra-acinary cellular proliferation and liquefaction of colloid matter. Extensive lymphocytic infiltration separates remnants of thyroid tissue. Acini show a lining of cylindric epithelium.

sometimes subdivided into smaller lobules, which appeared rather cirrhotic. Some of the acini were separated from one another by intralobar connective tissue and dense lymphocytic and plasmocytic infiltrations. The epithelial lining was cuboid in some places, cylindric in some and polymorphic in others. The glandular vesicles contained some slightly basophilic, but mostly eosinophilic, colloid which was for the most part liquefied or vacuolated. In some places desquamated cells were seen. In some lobules, as well as in some interlobar connective tissue bands, lymphocytic aggregations formed follicle-like structures. These might contain remnants of thyroid tissue. In areas of denser inflammatory infiltration were observed epithelial polymorphism and intra-acinar cell proliferation (partly polymorphic), which filled the smaller thyroid vesicles. The arteries and veins of the thyroid did not present any unusual changes.

The histologic diagnosis was chronic thyroiditis (fig. 3).

Course.—The wound healed per primam. The patient had a surprisingly rapid recovery of his general health and an increase in weight. His nervousness, as well as all other symptoms except the exophthalmos, disappeared. Figure 1 *B* shows the patient almost a month after the operation. One and one-half years after the operation I was informed that he was still in good health. Myxedema was not noted.

COMMENT

Before discussing the possible association of chronic thyroiditis and primary thyrotoxicosis (exophthalmic goiter), I shall review briefly the different forms of inflammation of the thyroid and their relation to thyrotoxicosis.

1. Acute thyroiditis is often accompanied with thyrotoxicosis (de Quervain, Apelt, Breuer, Petenr, Crile, Dunguer, Walko and Hagen). Histologically, morphologically and physiologically the thyroid tissue shows hyperactivity.

2. Subacute ("giant cell") thyroiditis of the de Quervain type, also classified as chronic thyroiditis by Vaux,[13] may be accompanied with thyrotoxicosis. Weyeneth noted slight thyrotoxic symptoms in 3 cases. Vaux, who, as a unitarian, classified subacute and chronic forms under the same heading and stated that the various forms of subacute and chronic thyroiditis described by continental authors were different stages of the same disease, found slight degrees of thyrotoxicosis in 9 of 38 cases. In 14 cases she noticed myxedema.

3. Lymphadenoid goiter usually causes myxedema (in 50 per cent of the cases according to American authors and in 2 of 8 cases according to Weyeneth).

4. With Simmonds' fibrous atrophy of the thyroid no thyrotoxic symptoms are observed.

5. The classic symptoms of primary thyrotoxicosis (exophthalmic goiter) associated with chronic thyroiditis were described for the first time in 1915 by Brünger.[14] Unfortunately, it has been impossible to obtain a copy of the author's original article. Brünger observed in 2 female patients histologic evidence of chronic thyroiditis. Neither of the patients survived operation.

Simmonds[15] expressed disagreement with Brünger's conception. He stated that there was no relation between exophthalmic goiter and chronic thyroiditis. Wegelin, who stated the belief that the occurrence of thyrotoxicosis in association with acute thyroiditis was almost classic, did not exactly object to Brünger's conception but stated that the association was exceptional. Giovanola[16] also denied a relation between the two conditions. More recently Kreuzbauer,[17] McClintock, Lee[18] and Weyeneth noted thyrotoxic symptoms, such as loss of weight, tremor, increase of the basal metabolic rate to + 25 and + 45 and slight nervousness, in cases of chronic thyroiditis. In a statistical examination of the cases observed in de Quervain's clinic (1918-1933), Wallis[19] found 100 cases of chronic thyroiditis among 4,148 in which operation was performed on the thyroid. In 15 of these cases there were thyrotoxic symptoms, such as slight or pronounced exophthalmos, tremor and palpitation; loss of weight was noted in 1 instance. Urban[20] noted 1 case of chronic thyroiditis among 4,250 cases in which the thyroid gland was examined. Enderlen[20] observed 1 case among 3,296 cases in which the thyroid was examined. Neither of them observed any signs of exophthalmic goiter.

Shaw and Smith found 48 cases of chronic thyroiditis among 10,500 cases in which thyroidectomy was performed at the Mayo Clinic. Among these, together with their personal cases, a total of 71 cases of chronic thyroiditis, they could not find a single instance in which there were symptoms of primary thyrotoxicosis.

Austen, Oehler and Bruck stated that in some cases of chronic thyroiditis thyrotoxic symptoms may be observed.

13. Vaux, D. M.: J. Path. & Bact. **46**:441, 1938.

14. Brünger, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **28**:213, 1914; cited by Reist[5] and by Giovanola.[16]

15. Simmonds, M.: Virchows Arch. f. path. Anat. **246**:140, 1923.

16. Giovanola, C.: Contribution à l'étude de la thyroïdite chronique, Thesis, Lausanne, Impr. Borgeaud, 1930.

17. Kreuzbauer, F. H.: Arch. f. klin. Chir. **166**: 178, 1931.

18. Lee, J. G.: Chronic Nonspecific Thyroiditis, Arch. Surg. **31**:982 (Dec.) 1935.

19. Wallis, A. E.: Chronic Thyroiditis: Comparative Analysis of One Hundred Cases, Arch. Surg. **33**: 545 (Oct.) 1936.

20. Cited by Weyeneth.[8a]

Weyeneth[21] mentioned that lymphadenoid goiter may show initial signs of thyrotoxicosis (in 50 per cent of his cases), which may be taken as *Basedow fruste,* but that Hashimoto's struma never causes the symptoms of a fully developed exophthalmic goiter. The same author,[21] in a personal communication, stated that in carefully examined material in cases of various types of chronic thyroiditis he had not observed a case of primary thyrotoxicosis.

Although several authors observed symptoms of a hyperfunctioning thyroid, Brünger was the only one before me to note primary thyrotoxicosis (exophthalmic goiter), with its cardinal symptoms, associated with chronic thyroiditis. On the other hand, the majority of authors stated that there is no relation between the two conditions. The case presented in this paper throws new light on the problem. Histologic examination showed undeniably morphologic evidences of chronic thyroiditis combined with signs of hyperfunction, which persisted in spite of the intake of large doses of iodine. Clinically the presence of exophthalmic goiter, with its cardinal and other symptoms, was just as certain. The symptoms consisted of an increase in the basal metabolic rate to + 87 per cent, pronounced exophthalmos, tremor, sinus tachycardia, loss of weight and attacks of diarrhea. This case demonstrates undeniably the association of the two conditions.

21. Weyeneth, R.: Personal communication to the author, 1943.

SUMMARY

In the first operative case of chronic thyroiditis observed in Turkey the cardinal and other symptoms of primary thyrotoxicosis (exophthalmic goiter) were clinically apparent. The diagnosis of the pathologist, Dr. Perihan Cambel, was chronic thyroiditis with histologic signs of hyperfunction of the thyroid. A review of the literature and the present case indicates that the association, even if rare, of histologically evident chronic thyroiditis and a fully developed exophthalmic goiter does exist.

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CONTINUOUS SPINAL ANESTHESIA

OBSERVATIONS ON 1,200 PATIENTS

R. C. MARTIN, M.D.; H. LIVINGSTONE, M.D., AND V. WELLMAN, M.D.
CHICAGO

Continuous, fractional or serial spinal anesthesia, since its introduction by Lemmon [1] on April 10, 1939, has been discussed in several publications, including, among others, those of Popova,[2] Nicholson,[3] Tuohy,[4] Hand and Schuhmacher,[5] Leigh and Burford,[6] Haugen, Ruth and Taylor,[7] Ansbro and Pico,[8] Lundy and his associates,[9] Apgar,[10] Fraser,[11] Hale and Shaar [12] and Lemmon and Hager.[13]

The interest in and the usefulness of this type of anesthesia have prompted us to report a series of 1,200 patients on whom operation was performed during continuous spinal anesthesia. A complete study, including adequate postoperative observations, has been made on the first 563 consecutive patients.

From the Department of Surgery, the University of Chicago.

1. Lemmon, W. T.: A Method for Continuous Spinal Anesthesia, Ann. Surg. **111**:141-144 (Jan.) 1940.
2. Popova, A. F.: Experimental Studies on Fractional Lumbar Anesthesia, Vestnik khir. **59**:101-108 (Jan.) 1940.
3. Nicholson, M. J.: Continuous Spinal Anesthesia, Lahey Clin. Bull. **2**:34-37 (Oct.) 1940.
4. Tuohy, E. B.: Continuous Spinal Anesthesia, Proc. Staff Meet., Mayo Clin. **16**:257-259 (April 23) 1941; Continuous Spinal Anesthesia: Its Usefulness and Technic Involved, Anesthesiology **5**:142-148 (March) 1944.
5. Hand, L. V., and Schuhmacher, L. F.: Pontocaine-Glucose Solution for Fractional Spinal Anesthesia, Lahey Clin. Bull. **2**:167-173 (Oct.) 1941.
6. Leigh, H., and Burford, G. E.: Simplified Equipment for Continuous Spinal Anesthesia, Anesth. & Analg. **20**:358-359 (Nov.-Dec.) 1941.
7. Haugen, F. P.; Ruth, H. S., and Taylor, I. B.: Serial Spinal Anesthesia, Anesthesiology **3**:52-60 (Jan.) 1942.
8. Ansbro, F. P., and Pico, L. J.: Continuous Spinal Anesthesia, Am. J. Surg. **55**:504-508 (March) 1942.
9. Lundy, J. S.; Tuohy, E. B.; Adams, R. C.; Mousel, L. H., and Seldon, T. H.: Annual Report for 1941 of the Section on Anesthesia, Proc. Staff Meet., Mayo Clin. **17**:225-238 (April 15) 1942.
10. Apgar, V.: Continuous Spinal Anesthesia, Anesthesiology **3**:522-529 (Sept.) 1942.
11. Fraser, R. J.: Continuous Lumbar Anesthesia, Anesth. & Analg. **22**:38-45 (Jan.-Feb.) 1943.
12. Hale, D. E., and Shaar, C. M.: Continuous Spinal Anesthesia, Anesthesiology **5**:53-60 (Jan.) 1944.
13. Lemmon, W. T., and Hager, H. G.: Continuous Spinal Anesthesia: Observations on Two Thousand Cases, Ann. Surg. **120**:129-142 (Aug.) 1944.

Procaine hydrochloride was employed as the anesthetic agent in this series, since, as Lemmon pointed out, its relative toxicity is less than that of metycaine hydrochloride, tetracaine hydrochloride or nupercaine hydrochloride. Procaine hydrochloride both as a 10 per cent solution and as crystals was used, and no difference in effectiveness between the two preparations was noted. The procaine was dissolved in the patient's spinal fluid, making a 5 per cent solution. Occasionally additional doses consisted of procaine hydrochloride dissolved in sterile isotonic solution of sodium chloride or distilled water to make a 5 per cent solution.

A brief review of our method of management follows:

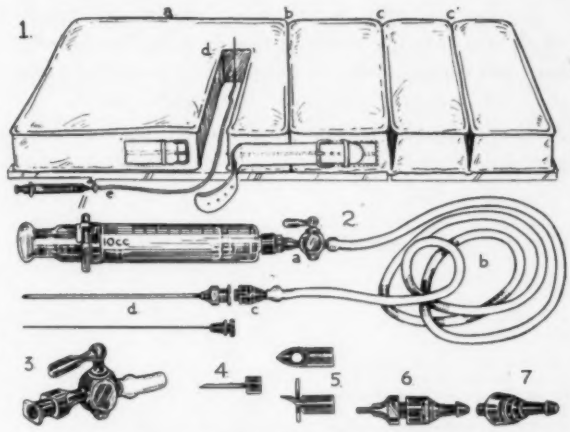
METHOD OF MANAGEMENT

Premedication.—Calcium pentobarbital and morphine were given one to one and one-half hours before operation. The average adult who was considered a fairly god risk received calcium pentobarbital in doses of from 0.18 to 0.27 Gm. in 50 cc. of water through the rectum if no pathologic condition of the rectum was present, and 0.01 Gm. of morphine sulfate was given by hypodermic injection. This dose was decreased for the aged, extremely ill and other patients considered poor risks. Subsequent injections of morphine were administered subcutaneously or intravenously, when indicated, during long operative procedures.

Technic.—The patient was placed on a rubber-covered mattress (figure), which is 6 feet (183 cm.) long, 18 inches (46 cm.) wide and 5 inches (13 cm.) thick. The mattress has a cutout area, 7 inches (18 cm.) in length and 6 inches (15 cm.) in width, that fits under the lumbar portion of the spine when the patient is supine. This mattress is constructed in sections for use when the patient is in various positions. Extra long metal holders for shoulder braces are needed because of the thickness of the mattress. Shoulder braces are essential to prevent displacement of the spinal needle when some degree of the Trendelenburg position is employed to obtain a high block. The patient was placed in the left lateral decubitus position for the lumbar puncture. With aseptic technic, a 1 per cent solution of procaine hydrochloride and ephedrine sulfate was injected locally over either the second or the third lumbar interspace. Nine patients in this series received no ephedrine because of extreme hypertension. For patients with a blood pressure of 180 mm. of mercury or more, ephedrine was omitted entirely, or a solution containing 0.024 to 0.049 Gm. of ephedrine sulfate was given intramuscularly after the lumbar puncture had been made and just before the procaine solution was injected. Such patients frequently have a labile blood pressure, which may fall 40

to 130 mm. of mercury when no ephedrine is given. The average patient received 0.049 Gm. of ephedrine sulfate. If hypotension was present after the initial administration of ephedrine, the dose was repeated before the spinal injection was made.

A Sise introducer was used to puncture the skin and make a point of entrance for the malleable German silver spinal needle. Such needles are made in three sizes: 17, 18 and 19 gage; they vary in length from 3½ to 4 inches (9 to 10 cm.). It is advisable to use as short a needle as possible in order to decrease the likelihood of its displacement when the patient is turned. On the other hand, for extremely obese patients the longest needle is necessary, and even then there may be displacement outward by the excess soft tissues when the patient is placed supine. When a successful lumbar puncture had been made, a 10 cc. Luer-Lok syringe was connected with the hub of the needle. From the average patient undergoing a long surgical procedure 4 cc. of spinal fluid was withdrawn in a first syringe, 4 cc. in a second syringe and 2 cc. in a third syringe. Equal parts of 10 per cent solution of procaine hydrochloride and spinal fluid were mixed, giving a 5 per cent solution of the drug, each cubic centimeter of which contained 50 mg. of procaine hydrochloride. When crystals were employed, 2 cc. of



Equipment used for continuous spinal anesthesia (reproduced with the permission of Dr. William T. Lemmon). *1*, table pad in sections (*a*, *b*, *c*, *c'*), with illustrations of the position of the spinal needle (*d*), the tubing (*e*), the stopcock and the syringe. *2*, Luer-Lok syringe connected to the stopcock (*a*), the rubber tubing (*b*), the Luer-Lok connection (*c*) and the spinal needle (*d*). *3*, close-up view of the stopcock. *4*, needle introducer for puncturing the skin. *5*, short bevel and counter opening in the lumbar puncture needle. *6*, plug for the spinal needle, to prevent loss of cerebrospinal fluid. *7*, Luer-Lok plug.

spinal fluid was used to dissolve each 100 mg. of crystals. The syringe was then attached by means of a stopcock to 30 inches (76 cm.) of thick-walled, small bore rubber tubing. The stopcock was opened; the tubing was held above the level of the syringe, and 2 cc. of the mixture was forced into the tubing to displace air completely and fill the lumen. The stopcock was then closed, and the Luer-Lok connection on the distal end of the tubing was connected with the spinal needle. Since the operations in the present series were all major surgical procedures, mainly laparotomies, the average initial dose was 150 mg. of procaine hydrochloride (3 cc.), injected at the rate of about 0.5 cc. per second. Judgment must be used in determining the rate of injection for the individual patient, which should depend on the patient's general condition, the length of the spine and the height of anesthesia required; a slower rate is advisable for a patient who is considered a poor risk or for low block. A larger initial dose was employed only for extremely obese persons or for patients with gross deformity of the spinal column with which the hazard of displacement of the needle during changes in position was great. The initial injection never exceeded 1.5 mg. of procaine hydrochloride per pound (0.5 Kg.) of body weight, and usually it was 1 mg. or less per pound of body weight. Some authors have reported the use of a smaller initial dose. Since intra-abdominal relaxation was necessary for most of the patients in this series, an initial dose sufficient for exploration was provided.

Two assistants turned the patient from the lateral to the supine position, while the anesthetist held the syringe and tubing and directed the turning so that the needle was not displaced and lay free in the space provided in the mattress. The assistants slipped their hands under the patient's shoulders and hips, lifted him to the left edge of the table and then gently turned him to the supine position, making sure that the spine was not twisted at any time. Shoulder braces were used; the needle was watched when the Trendelenburg position was established, and the table was kept on a straight plane at all times to prevent dislocation of the spinal needle. The syringe was secured with a butterfly adhesive tape a few inches to the right of the patient's head.

The blood pressure, pulse rate and respiratory rate were recorded every five minutes. The table was kept flat for five minutes after the injection. If the level of anesthesia obtained was not high enough at the end of this time the table was placed in varying degrees of the Trendelenburg position until the desired level was reached. An additional 1 cc. (50 mg. of procaine hydrochloride) of the procaine–spinal fluid solution was injected rapidly if the block was not high enough at the end of ten minutes. We did not employ barbotage, since this method makes it impossible to calculate the concentration of the remaining solution, as well as the level of anesthesia. The average patient required additional injections of 50 mg. each at the end of approximately the first hour and usually every thirty minutes thereafter.

The underlying principles of spinal anesthesia must be observed throughout the procedure if the administration of continuous spinal anesthesia is to be successful. Dispersion, convection and diffusion must be considered when anesthetic solutions are injected into the subarachnoid space. The relation of the specific gravity of the solution to the spinal fluid is important. A 5 per cent solution of procaine hydrochloride and spinal fluid is hyperbaric, having a specific gravity of 1.015, as compared with 1.007 for the spinal fluid. The position of the patient during the first ten to fifteen minutes after the anesthetic solution is injected must be carefully controlled in order to localize the block correctly. The height of anesthesia can also be affected by the site of injection, the length and caliber of the patient's spinal canal and the rate of injection of the anesthetic solution. Since additive amounts of the drug are usually only 1 cc. in volume, this small quantity will not give a high block unless the rate of injection is rapid and the patient is in the proper position.

It must also be remembered that the sensory roots are more susceptible to the anesthetic solution than are the motor roots. Since the sensory root fibers are blocked in the following sequence, i. e., fibers carrying pain, touch, temperature and muscle sense and, finally, visceral sensory fibers from the sympathetic system, it seems reasonable to assume that unpleasant sensations or actual pain which are occasionally produced by traction on the viscera are probably due to the unparalyzed sympathetic pathways. In such a situation supple-

mentary gas anesthesia and adequate oxygenation usually control the situation. If pentothal sodium is given intravenously, it should be administered in only minute amounts, just sufficient to keep the patient drowsy and euphoric. Inhalations of oxygen should be given at the same time. Administration of pentothal sodium sufficient to produce unconsciousness introduces the additional hazard of regurgitation and aspiration during surgical procedures on the upper portion of the abdomen.

A fall in blood pressure is frequently followed by nausea or vomiting, due to lack of oxygenation of the vomiting center. It is therefore of greatest importance to ascertain promptly any evidence of anoxia, such as occurs with a high intercostal block or fall in blood pressure, and to begin oxygen inhalation immediately before disturbing manifestations, such as nausea or vomiting, occur.

Postoperative Care.—The patient was kept flat in bed without a pillow for twenty-four hours. During the past year early rising has been practiced in two surgical services, in which all patients who are able are urged to become ambulatory twenty-four to forty-eight hours after operation. So far, there have been no disturbing manifestations, such as headache, from this practice.

After operation the blood pressure, pulse rate and respiratory rate were recorded every fifteen minutes for two hours and thereafter at longer intervals, if indicated. Oxygen therapy was administered to any patient having evidence of surgical shock from massive intra-abdominal resection or hemorrhage.

COMMENT

Since the University of Chicago is a teaching institution and surgery interns, as well as anesthesia residents, are being trained, spinal anesthesia was administered to the first 563 patients by a total of twenty-seven persons. This factor should be considered in evaluation of the results.

Age.—The age of the first 563 patients varied from 18 to 86 years, with 276 in the 40 to 60 year group. Thirty-three patients were from 70 to 79 years old, and 3 were over 80 years of age. Approximately 17 per cent of these patients were considered as poor or serious risks for operation, while 41 per cent were only fair surgical risks.

Preoperative Complications.—Hypertension, arteriosclerosis, heart disease of various types, anemias of varying severity, jaundice, serious debility, marked obesity, diabetes mellitus and pulmonary tuberculosis made up the bulk of the preoperative complications. Four patients had pernicious anemia and 3 had latent syphilis. While several of these conditions are considered by many persons as contraindications to spinal anesthesia, in our evaluation of the patients and of the surgical procedures contemplated, spinal anesthesia seemed to us a lesser evil than general anesthesia of the length and depth that would have been required.

Duration and Height of Anesthesia.—The duration of the anesthesia was from one and one-half to three hours in 72 per cent of the patients. In most instances the level of anesthesia extended as high as the seventh or the fourth dorsal nerve roots. Fifty-two operations, or 9 per cent, lasted from three to four hours; 16, or 4 per cent, from four to five hours, and 4, or 7 per cent, for more than five hours. The longest operative procedure in our series, a total pancreatectomy, lasted seven hours and forty-five minutes.

TABLE 1.—*Total Dose of Procaine Hydrochloride*

Time	Minimum, Mg.	Maximum, Mg.	Average, Mg.
Less than 1 hour	120	350	154
Less than 1½ hours	125	500	209
Less than 2 hours	150	500	269
Less than 3 hours	200	675	341
Less than 4 hours	200	700	425
Less than 5 hours	250	1,050	525
Less than 8 hours	...	900	...

Dosage.—Table 1 gives the minimum, maximum and average doses of procaine hydrochloride for operations of stated lengths. The initial dose of 150 mg. of procaine hydrochloride is far greater than that used in some clinics and was perhaps excessive for the shorter surgical procedures. However, because of the need for good intra-abdominal relaxation in these patients and because of the chance that the needle might be dislodged when the patient was turned, we felt that this dose was desirable.

TABLE 2.—*Types of Operation Performed on 1,200 Patients Under Continuous Spinal Anesthesia*

	First Series of 563 Operations	Total Number of Operations
Operations on the biliary tract	148	310
Resection of stomach	63	128
Other operations on stomach	17	42
Repair of diaphragmatic hernia	1	1
Repair of incisional hernia (upper abdominal)	27	55
Exploratory laparotomy and biopsy (inoperable condition)	55	91
Operations on pancreas, etc.	15	38
Splenectomy	7	13
Intestinal resections, etc.	72	198
One stage abdominoperineal resection of rectum	15	37
Perineal excision of carcinoma of rectum	2	2
Appendectomy	53	99
Gynecologic operations (intra-abdominal)	8	20
Operations on kidney, bladder or ureter	4	20
Inguinal or femoral herniotomy (many hernias were bilateral; 5 were strangulated)	34	90
Miscellaneous abdominal resections (retroperitoneal, adrenal, etc.)	42	49
Operations on lower extremities (excision of aneurysm or large tumor)	..	7
Total number of operations	563	1,200

Operative Procedures.—Operation on the biliary tract, gastric resection, exploratory laparotomy and intestinal resection were the operations of greatest frequency. Table 2 pres-

ents the operative procedures for the entire series, as well as for the first 563 patients discussed. The brief headings do not give an accurate picture of the extensive resections done for advanced malignant growths, which made up a relatively large per cent of the total number of operations. For instance, the heading "Operations on pancreas, etc." usually included two or more of the following procedures: gastrectomy, splenectomy, partial hepatectomy, adrenalectomy and various intestinal resections.

Anesthetic Agents.—For 65 per cent of the patients in this series procaine hydrochloride or procaine hydrochloride together with inhalation of oxygen was employed. For the remaining 35 per cent it was necessary to supplement the anesthetic with nitrous oxide and oxygen, ethylene and oxygen or ethylene oxygen and ether; and in a few cases procaine hydrochloride infiltration was employed, or pentothal sodium injected intravenously in 2.5 per cent solution. Nitrous oxide and oxygen were given to 12 per cent of the patients; ethylene and oxygen, to 14 per cent; nitrous oxide and oxygen supplemented with ethylene and oxygen, to 2 per cent; ethylene, oxygen and ether, to 4 per cent, and procaine hydrochloride infiltration or intravenously administered pentothal sodium, to 3 per cent. Supplementary anesthesia was necessary for the comfort of nervous, apprehensive persons and for patients having persistent nausea and emesis during operations on the upper portion of the abdomen, due to traction on the mesentery or in the area of the gallbladder or to manipulation of the stomach. Gas and ether were given to 20 patients (3.5 per cent) because of partial or complete failure of the anesthetic or inadequate relaxation. In some of these patients spinal fluid could be freely withdrawn and injected, but no anesthesia resulted. In the remainder of these patients with unsatisfactory anesthesia, the needle became dislodged when the patient was placed supine or during changes in position during the surgical procedure.

Complications During Anesthesia.—Nausea and emesis were the most frequent complications encountered during anesthesia. They were observed in 17 per cent of the patients; in most instances they occurred during exploration of the upper part of the abdomen and were associated with a fall in blood pressure. Several apprehensive and psychoneurotic persons vomited intermittently during less extensive procedures. The average fall in blood pressure attributable to the anesthetic was 11 mm. of mercury and occurred five to fifteen minutes after the initial injection. Subsequent fall in blood pressure occurred in a number of patients when the peritoneum was opened and exploration was begun. This effect is comparable to that observed during similar manipulations under inhalation agents. In 6 per cent of the patients the blood pressure fell to shock levels during vigorous exploration of the upper portion of the abdomen. Inhalation of oxygen and subcutaneous or intravenous injections of ephedrine sulfate, the choice depending on the extent of the drop, were administered for the fall in blood pressure due to the exploration, and satisfactory results were obtained. Blood or plasma was used to combat a decrease in blood pressure due to hemorrhage. As much as 4,000 cc. of whole blood was given during a single operation.

Pain in the shoulders was severe and persistent in a few patients during manipulation in the area of the gallbladder.

Complete paralysis of the intercostal muscles due to a high block occurred in 1 patient. Recovery was uneventful after the use of oxygen inhalations and ephedrine.

Postoperative Complications. — Postoperative nausea and emesis occurred in 7 per cent of the patients of this series. While these complications were usually of brief duration, they sometimes persisted for two or three days, until medication with opiates was discontinued. Distention was present in 2.7 per cent. Impaired hepatic function, as determined by the level of prothrombin, total proteins, cholesterol and cholesterol esters in the blood, was present in 2.2 per cent of the patients. In each of these patients hepatitis was present at the time of the operation.

Twenty-five patients, or 4.4 per cent, had postoperative pulmonary complications. Five, or 0.9 per cent, had lobar pneumonia, and 12, or 2.1 per cent, bronchopneumonia. Pneumonia developed one to three days after the surgical procedure in several patients, most of whom had been considered poor risks before operation. Atelectasis occurred in 8 patients, or 1.4 per cent.

In only 2 patients was there a postanesthesia fall in blood pressure of any consequence, and in neither of these did the pressure fall to shock levels. From this group we excluded those with postoperative hemorrhages.

The incidence of urinary retention was 4 per cent and that of cystitis 2 per cent. Rarely was retention present more than two to three days.

Eleven patients, or 2 per cent, complained briefly of postoperative backache and 12, or 2.1 per cent, of headache. Some, but not all, of the patients with headache sat up on the day of operation, in spite of careful instructions to remain flat in bed without a pillow for twenty-four hours.

Four days after an "interval appendectomy" in which a normal appendix was removed, a 24 year old woman complained of severe headache and had a positive Kernig sign. These symptoms gradually disappeared, but at the time of her discharge from the hospital, on the tenth postoperative day, there was still cervical pain when she sat up. There was no postoperative fever or elevation of the white cell count. The clinical diagnosis was aseptic meningitis following spinal anesthesia. A rapid and uneventful lumbar puncture had been performed and 150 mg. of procaine hydrochloride in 3 cc. of spinal fluid injected. The level of the anesthesia reached the sixth dorsal nerve root, and the operation lasted only fifteen minutes. Spinal fluid withdrawn before the anesthetic solution was injected contained a few red blood cells and 2 lymphocytes per cubic millimeter. No postoperative lumbar puncture was performed.

TABLE 3.—*Death Occurring After Continuous Spinal Anesthesia in 563 Patients*

No.	Deaths, %	Cause of Death	Interval Between Operations and Death: Day of Operation	1-3 Days	4-7 Days	7-14 Days	14-21 Days	Within 1 Month	Within 2 Months
6	1.06	Cancer of pancreas	..	..	2	..	1	1	2
4	0.71	Cancer of stomach	..	1	1	..	1	..	1
2	0.35	Cancer of colon	..	..	..	..	1	..	1
1	0.18	Cancer of gallbladder and liver	..	..	..	..	..	..	1
7	1.2	Peritonitis	..	1	2	3	1	..	..
1	0.18	Other gastrointestinal disease	..	..	..	..	1	..	..
5	0.88	Hepatic damage	..	1	2	2	..	..	..
3	0.5	Pneumonia	..	1 (broncho-pneumonia)	1 (lobar pneumonia)	..	..	..	1 (broncho-pneumonia)
2	0.35	Aspiration of vomitus	..	..	1	1	..	..	..
2	0.35	Pulmonary emboli	..	..	..	..	1	1	..
2	0.35	Circulatory failure	2	..	..	..	..	..	..
3	0.5	Traumatic shock	..	3	..	..	..	..	..
1	0.18	Coronary occlusion	..	..	..	1	..	..	..
2	0.35	Postoperative hemorrhage	..	1	..	1	..	..	..
1	0.18	Cerebral accident	..	1	..	..	..	..	..
1	0.18	Hepatorenal failure	..	..	1	..	..	..	..
2	0.35	Cardiac failure	..	1	..	1	..	..	..
1	0.18	Uremia	..	..	1	..	..	..	..
46	8	Total	2	10	11	9	6	2	6

Deaths.—Table 3 summarizes the postoperative deaths. There were 46 deaths in this series of 563 patients, giving a mortality rate of 8 per cent. Thirty-three of the deaths occurred in patients who had malignant disease. There were no fatalities in the operating room.

Five patients died of hepatic damage, one to fourteen days after operation. The youngest of these patients was a man aged 38 with biliary cirrhosis, who was subjected to an exploratory laparotomy and a choledochoenterostomy. He died on the second postoperative day. The remainder of the group were over 50 years of age and had cirrhosis of the liver or hepatitis at the time of operation.

Coronary occlusion occurred on the eighteenth postoperative day in a 51 year old man with recurrent carcinoma of the cecum. The patient was emaciated and nervous and was considered a poor operative risk. A radical resection of the abdominal wall and a portion of the small intestine together with removal of the right kidney was performed in two hours and forty-five minutes. There was considerable hemorrhage. The normal blood pressure was 134 mm. of mercury systolic and 80 mm. diastolic. The blood pressure was not obtainable for thirty minutes two hours after the operation began in spite of liberal parenteral administration of blood and saline solution. While the abdomen was being closed, the blood pressure rose to 110 systolic and 80 diastolic and was at this level when the patient left the operating room. On the eighth postoperative day the wound broke down and became infected with Bacillus pyocyaneus. The patient became progressively weaker and died suddenly on the eighteenth postoperative day. Postmortem examination revealed complete occlusion of the anterior descending branch of the left coronary artery with a thrombus.

Circulatory failure occurring three hours after operation accounted for the death of 2 patients. Both patients had extensive malignant lesions, bled profusely and went into surgical shock during a pancreatoduodenectomy and a resection of the stomach respectively.

Two extensive hemorrhages were observed. The first of these occurred twenty-four hours after excision of the gallbladder, the common duct and the hepatic duct in a 59 year old man with carcinoma of the hepatic duct. The second was from the operative wound on the eleventh day in a patient with a large metastatic abdominal tumor.

Peritonitis accounted for the deaths of 7 patients, occurring six to eleven days after opera-

tion. Terminal bronchopneumonia developed in 2 of these patients.

A 64 year old woman with carcinoma of the sigmoid had a cerebral accident three days after drainage of a retrouterine abscess, an end to end anastomosis and a loop colostomy. The patient had generalized arteriosclerosis, a blood pressure of 160 mm. of mercury systolic and 100 mm. diastolic and a history of a cerebral accident in 1938. No rise in blood pressure occurred during the surgical procedure.

Hepatorenal failure on the sixth postoperative day caused the death of a 70 year old woman who had carcinoma of the head of the pancreas with extensive metastases to the liver. An exploratory laparotomy was performed without untoward effects, but heart failure began ten hours after the operation. Digitalization was carried out, and improvement was noted, until the patient became anuric on the third postoperative day.

Cardiac failure was the immediate cause of death of 2 patients. One of these, a 72 year old woman with carcinoma of the rectum, had a preoperative blood pressure of 164 systolic and 80 diastolic, hypoproteinemia (4.54 Gm. of total protein per hundred cubic centimeters of blood) and a history of heart failure ten years previously. The first stage of a combined abdominoperineal resection was performed, with the patient under spinal anesthesia, without deleterious effects. Four days later she was given spinal anesthesia for the second stage. Ten minutes after intraspinal injection of 150 mg. of procaine hydrochloride the patient went into shock. Inhalation of oxygen and intravenous injection of 0.024 Gm. and intramuscular injection of 0.024 Gm. of ephedrine sulfate restored the blood pressure to its former level, and the operation proceeded. Fibrillation began on the afternoon of the operative day. Heart failure began in six days, and she became progressively worse in spite of administration of oxygen and digitalis. Death occurred on the sixteenth day; postmortem examination revealed hydrothorax, pulmonary edema and coronary arteriosclerosis.

The other patient, an emaciated man aged 67, had carcinoma of the head of the pancreas with pleural and hepatic spread. This patient had obstructive jaundice, auricular fibrillation, ascites, secondary anemia, nutritional edema and a massive hydrothorax on the left side. He was dyspneic and gasping for breath before the spinal anesthetic was administered. During a pancreatoduodenectomy and a complete resection of the pancreas, which lasted four hours and forty minutes, 550 mg. of procaine hydrochloride was given. Oxygen was administered throughout the procedure. The blood pressure fell to 60 mm. of mercury systolic and 40 mm. diastolic twenty minutes after the operation began and remained low throughout. Thirty-seven hundred cubic centimeters of blood and 1,500 cc. of saline solution were given intravenously. Heart failure, with pulmonary edema, oliguria and hyperglycemia, followed. Oxygen was administered. The patient died on the second postoperative day, while a thoracentesis was being performed.

The immediate cause of death of 3 patients was lobar pneumonia or bronchopneumonia. Gastroenterostomy was performed on an emaciated 47 year old man with a stenosing duodenal ulcer and nonspecific ulcerative colitis. Peritonitis developed on the fourth postoperative day and pneumonia on the fifth. The patient died on the sixth postoperative day.

An anemic woman aged 68 with carcinoma of the gallbladder underwent a three hour operation consisting of exploratory laparotomy and excision of a specimen of the tumor for biopsy. Pneumonia developed on the first postoperative day, and death occurred on the third postoperative day.

The third case of pneumonia developed two months after operation and had no relation to the anesthesia.

One death, due to aspiration pneumonia, occurred in an 83 year old man who had a combined abdominoperineal resection for carcinoma of the rectum. Two days after the operation the patient was nauseated and vomited. A cough productive of thick sputum followed this episode. The colostomy became necrotic three days later; so its gangrenous portion was removed and a new colostomy opening established, with the operative area under local anesthesia. The patient sank into a comatose state and died later the same day. Postmortem examination of the lungs revealed areas of leukocytic consolidation with edema. In some places there were gangrenous areas, with little surrounding inflammatory reaction. The bronchioles were filled with an exudate; there was extensive bacterial colonization, and the mucosa was ulcerated.

SUMMARY

The clinical experience gained from employment of continuous spinal anesthesia with 1,200 patients has led to the following impressions and conclusions: Excellent muscular relaxation and prolonged operating time make this type of anesthesia increasingly popular with surgeons. After operation, during the first twelve to twenty-four hours, the patients are generally in better condition than they are after inhalation anesthesia

of second or third plane depth. They are rational and cooperative and have a minimal amount of the fluid imbalance resulting from nausea, emesis and diaphoresis. Urinary retention and abdominal distention occur frequently. A minimum of nursing care is required, since the patient is awake and relatively comfortable; also, the dangers of respiratory obstruction or of aspiration of vomitus are practically removed.

A wide variation in individual requirements of procaine was noted in this series. One patient was given 1,050 mg. of procaine hydrochloride in five hours, while another required only 900 mg. for an operation lasting seven hours and forty-five minutes. Absence of anesthesia when spinal fluid could be freely withdrawn and reinjected was puzzling in the few cases in which it was noted. No doubt, with a long-beveled needle there is still the possibility of part of the injection being made into the peridural area.

Light supplementary anesthesia, induced with one of the anesthetic gases or with intravenously administered pentothal sodium, was sometimes desirable for the comfort of the patient during a surgical operation on the upper part of the abdomen. This "combined anesthesia" was also valuable for very nervous persons undergoing long procedures, while the spinal block provided the necessary intra-abdominal relaxation.

A number of patients in this series were poor candidates for any type of anesthesia or operative procedure. While local anesthesia would have been less hazardous for them than spinal anesthesia, it would not have provided adequate relaxation for the operation that was to be performed.

No residual paresis or paresthesia was noted in our series, although the spinal needle remained in the subarachnoid space from three to five hours in many instances.

There was a low incidence of anesthesia complications among the 46 persons who died (8 per cent) after the first 563 operations. As can be seen in table 2, the death rate has decreased since the first 563 surgical procedures, owing to the increased use of continuous spinal anesthesia for less extensive procedures, such as repair of inguinal and femoral hernias and operations on the lower portion of the abdomen.

The underlying principles of spinal anesthesia must be scrupulously observed throughout the surgical procedure if the method for continuous spinal anesthesia is to be successful.

THROMBOPLASTIC REAGENT

DEVELOPMENT OF A MORE SUITABLE PREPARATION FOR MEASURING ACCELERATED CLOTTING TENDENCY AND FOR USE FOLLOWING ADMINISTRATION OF DICOUMARIN (3,3′-METHYLENE-BIS-[4-HYDROXYCOUMARIN])

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BALTIMORE

It is a well established fact that in certain clinical conditions, especially those following surgical procedures and trauma, the equilibrium of the coagulation elements of the blood is shifted to a state favorable to clotting.[1] A laboratory procedure is needed for detecting this tendency to intravascular clotting before the appearance of thrombotic phenomena. If such a procedure were available to the clinician, in vivo anticoagulants, such as heparin or dicoumarin (3,3′-methylene-bis [4-hydroxycoumarin]), could be administered to patients having indications of such a tendency. Serious consequences and long periods of hospitalization could be averted in many instances. The introduction of dicoumarin,[2] however, has posed another problem, that of maintaining a precise control of the mechanism for blood coagulation in order to avoid hemorrhagic consequences following the use of this drug. Difficulty in maintaining a given clotting level, as well as undesirable results, including death, has been reported.[3]

A biochemical approach to the problem of detecting a tendency to intravascular clotting has been developed by two methods of investigating the coagulation reaction: (1) study of the prothrombin activity of serial dilutions of plasma,[4] and (2) study of thromboplastic activity by observing the effect of heparin on the clotting of whole blood.[5] With the use of dilute plasma in an adaptation of Quick's procedure, increased prothrombin activity has been demonstrated in the following clinical conditions: thrombophlebitis, post-traumatic, postoperative and postpartum states and gangrene.[6] The original method, however, gave no clue that it could be used for such a purpose, since Quick employed only normal plasma to construct his prothrombin activity curves. Resistance to intravenous administration of heparin [5a] has also been reported as an indication of increased coagulability of intracorporal blood. With the aid of a procedure for testing tolerance to heparin it has been pos-

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Prof. Alsoph H. Corwin, of the Department of Chemistry, the Johns Hopkins University, and Dr. Karl J. Brunings, of the Department of Chemistry, New York University, made suggestions as to the chemical problems involved.

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sible to correlate decreased response to heparin with the clinical conditions just mentioned. Recently another method [5b] has been reported, in which varying amounts of heparin are added to drawn blood to ascertain differential clotting rates. The results obtained with the two methods, using this anticoagulant, are comparable. It is especially noteworthy that these methods, employing an entirely different principle, yield information identical with that obtained with the procedure for determining prothrombin clotting time with dilute plasma.

MEASUREMENT OF PROTHROMBIN ACTIVITY

One approach to the solution of the problems of thrombophilia and control of the coagulative processes during administration of dicoumarin is the development of a critical and dependable laboratory technic for evaluating prothrombin activity. This procedure should be of such simplicity that any general hospital would be able to carry it out and obtain reliable and comparable results. Three methods for measuring prothrombin activity have been developed since Howell's noteworthy investigations,[7] i. e., the Quick,[8] Warner, Brinkhous and Smith [9] and Dam and Glavind.[10] Unfortunately, the values obtained with these procedures have not been satisfactorily interpolated, since the methods differ widely in principle.

Warner, Brinkhous and Smith [9] developed an elaborate two stage technic, which, they stated, takes cognizance of all the factors in the coagulation process. The prothrombin in a sample of defibrinated plasma is first completely converted to thrombin with thromboplastic substance derived from beef lung. Fibrinogen is then added to serial dilutions of the resulting thrombin solution until a given dilution yields a minimum clotting time. Results are expressed in terms of percentage of prothrombin. The complexity of the technical details involved has restricted its general application.

Dam and Glavind [10] used a standardized tissue extract and estimated prothrombin activity in terms of the amount necessary to induce coagulation in three minutes in a sample of blood which had been treated with heparin. This method, likewise, has found limited use.

Quick's [11] investigations yielded a widely used laboratory procedure for determining prothrombin activity of human plasma. This method involves the addition of an excess of thromboplastic substance, obtained from acetone-treated rabbit brain, in the presence of an optimum calcium ion concentration. The clotting time, in seconds, is considered to be a measure of the amount of prothrombin present. It has, in general, proved to be the most satisfactory technic to date and has the advantage of simplicity in application; also, it can be performed with minimum training and is readily adaptable to multiple determinations. Extensive use of this test has been made to study hemorrhagic diathesis, with satisfactory results. It can be more suitably adapted to follow prothrombin activity during administration of dicoumarin and to detect the clotting tendency of intracorporal blood. An attempt is made here to analyze and to define the factors involved.

MATERIAL AND METHODS

1. *Thromboplastic Substance.*—Quick's[11] method for the preparation of dehydrated rabbit brain was followed in detail. The meninges and the blood vessels were removed from fresh rabbit brains and quickly washed in isotonic solution of sodium chloride. The brain tissue was then transferred to a mortar containing anhydrous acetone and was macerated with a pestle. Fresh acetone was repeatedly added until a fine granular product was obtained. Ten changes of acetone should not require more than fifteen minutes. The resulting product was suspended in fresh acetone and poured over a suction filter. The treated material was washed on the filter with about 400 cc. of fresh acetone and allowed to dry by suction for thirty minutes. The filter was then transferred to a vacuum desiccator, evacuated and allowed to remain eight to ten hours. The dry material then presented a coarsely granular appearance. The product was stored in a tightly stoppered bottle in a refrigerator. Such a preparation kept its potency for two months under these conditions, without having to be sealed in ampules under vacuum.

(*a*) Quick's Thromboplastic Reagent: Quick's method of preparation is summarized as used in this investigation. Three hundred milligrams of the coarsely granular material, obtained according to the technic just described, was suspended in 5 cc. of 0.85 per cent saline solution containing 0.1 cc. of tenth-molar solution of sodium oxalate. After gentle stirring, the tube was placed in a water bath maintained at 50 C. and then incubated for fifteen minutes. After eight minutes the tube was gently agitated to resuspend the coarse particles. At the end of the incubation period the suspension was centrifuged at a slow speed for about

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9. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**:667, 1936.

10. Dam, H., and Glavind, J.: Determination of Vitamin K by the Curative Blood-Clotting Method, Biochem. J. **32**:1018, 1938.

11. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942.

ten seconds, when a translucent supernatant free from larger particles resulted. If, however, the dehydrated brain suspension was shaken at intervals during incubation, the resulting preparation frequently did not bring about coagulation of normal undiluted plasma in eleven to twelve seconds. A clotting time of twelve to fourteen seconds was obtained instead. However, when the reagent was properly prepared, Quick's values were consistently obtained during this investigation, namely, eleven to twelve seconds for normal undiluted plasma and thirty-four to thirty-six seconds for normal 12.5 per cent plasma (table 1).

(*b*) Recommended Thromboplastic Reagent (arbitrarily designated B. F.): A portion of the coarsely granular, acetone-dehydrated rabbit brain was placed in a mortar and ground dry with a pestle into a fine powder. Two hundred and fifty milligrams of this powder was suspended in 5 cc. of 0.85 per cent saline solution containing 0.1 cc. of tenth-molar solution of sodium oxalate. The tube was shaken to insure uniform distribution of the particles and placed in a water bath maintained at 50 C. The suspension was thoroughly shaken at two minute intervals during the total incubation period of fifteen minutes. At the end of this time the suspension was centrifuged twenty seconds to remove the coarser particles. A milky, opaque supernatant was obtained. This emulsion brought about the coagulation of normal undiluted plasma in thirteen to fifteen seconds and of normal 12.5 per cent plasma in eighty-five to ninety-five seconds (table 1). No difficulty was experienced in duplicating the desired clotting time for undiluted normal plasma. On some occasions, however, a clotting time of seventy to eighty seconds for 12.5 per cent plasma resulted. Such an emulsion can be corrected by resuspension of the residue by means of shaking and recentrifuging. This variability has been observed rarely.

2. *Calcium Chloride Solution.*—The concentration recommended by Quick in his earlier paper was 0.025 molar. This molarity was selected and used throughout the present investigation in conjunction with the modified thromboplastic reagent (designated as B. F.) that was developed.

3. *Technic.*—Four and one-half cubic centimeters of freshly drawn blood was introduced into a graduated centrifuge tube containing 0.5 cc. of tenth-molar solution of sodium oxalate. The tube was inverted several times and centrifuged to obtain clear plasma.

In the performance of the test, 0.1 cc. of clear plasma was placed in a small tube, to which 0.1 cc. of modified thromboplastic reagent (B. F.) was added. After thorough shaking of the contents, 0.1 cc. of 0.025 molar solution of calcium chloride was added to the mixture. A stopwatch was started and the tube placed immediately in a water bath adjusted to 37.5 C., in which it was tilted back and forth until the formation of a firm clot was observed. Normal undiluted plasma coagulated in thirteen to fifteen seconds.

Five-tenths cubic centimeter of clear, oxalated plasma was added to 3.5 cc. of 0.85 per cent saline solution to obtain a 12.5 per cent dilution. One-tenth cubic centimeter of this diluted plasma was pipetted into each of two small tubes. Thromboplastic reagent and calcium chloride solution (0.1 cc. each) were added to each one, and both tubes were placed in the water bath. They were tilted back and forth until a web clot appeared at the rim of the meniscus. Normal 12.5 per cent plasma clotted in eighty-five to ninety-five seconds. Usually, the two tubes showed a web clot simultaneously, but if small variations occurred, the two values were averaged.

FACTORS INVOLVED IN QUICK'S METHOD FOR DETERMINING PROTHROMBIN ACTIVITY

Two factors in Quick's method merit careful consideration: (1) the preparation and the coagulation-activating characteristics of the reagent possessing thromboplastic properties and (2) the selection of an optimum calcium chloride concentration. A review of the evolution of Quick's procedure reveals that changes have been introduced since it was first described.[12] The fact that revisions have been made suggests that the role of these two factors has not been completely explored.

Thromboplastin Reagent.—A survey of the available data reveals that this reagent affects the coagulation reaction to a pronounced degree and that its properties determine the characteristics of the prothrombin activity curve. Chart 1 shows curves having different trends, depending on the method of preparation and the source. Thromboplastic substance is not a chemically defined entity but a complex mixture of variable composition.[13] The biologic behavior of the material is only partially defined. It becomes necessary to rely on reproducibility of biochemical activity rather than on chemical characterization. The details of the method of preparation of this reagent are primary factors governing its reproducibility and applicability.

Several biologic sources of this substance have been investigated and are classified as follows: (1) rabbit brain: (*a*) acetone-treated tissue extracts,[14] (*b*) air-dried tissue extracts[15] and (*c*) fresh tissue extracts[16]; (2) beef and rabbit lung,[17] and (3) snake venom.[18] The choice of

12. Quick, A. J.: On the Various Properties of Thromboplastin (Aqueous Tissue Extracts), Am. J. Physiol. **114**:282, 1936; footnote 8.

13. Chargaff, E.: Lipoproteins, in Advances in Protein Chemistry I, New York, Academic Press, 1944.

14. Bingham, Meyer and Pohle.[20a] Brambel and Loker.[4] Butsch and Stewart.[20c] Page and Russell.[20d] Quick (footnotes 8 and 19 *b*). Stats and Bullowa.[20f]

15. Barker.[3c] Davidson and MacDonald.[20k] Magath.[20l] Shapiro and others.[20m] Souter and Kark.[20n]

16. Hause and Tocantins.[20g] Lucia and Aggeler.[20h] Quick.[19a] Ziffren and others.[20i]

17. Quick.[19a] Ziffren and others.[20i]

(Footnotes continued on page 141)

TABLE 1.—*Successive Clotting Times Obtained with the Quick and the Modified Thromboplastic Reagent for Patients with Various Clinical Conditions and for Normal Subjects*

	Thromboplastin				Thromboplastin				Thromboplastin				Thromboplastin				Thromboplastin				Thromboplastin				
	Quick		B. F.		Quick		B. F.		Quick		B. F.		Quick		B. F.		Quick		B. F.		Quick		B. F.		
	Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		Plasma Clotting Time, Sec.		
	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Undil.	12.5%	Clinical Conditions
1.....	12	35	14	85	12	27	14	68	12	25	13	62	11	32	14	85	12	30	15	95	12	36	14	95	Postoperative
2.....	12	34	13	90	11	24	14	63	12	23	13	58	12	26	14	69	12	32	14	76	12	33	13	86	Postoperative
3.....	11	29	14	95	13	23	15	64	14	40	17	105	12	32	14	62	12	29	13	64	12	38	14	88	Postoperative
4.....	12	32	13	78	12	24	13	52	12	28	13	66	12	29	14	62	12	30	14	65	12	29	13	75	Postoperative
5.....	12	34	13	55	12	22	13	47	13	23	13	54	12	24	13	54	11	28	13	52	12	36	13	60	Postoperative
6.....	12	36	14	95	12	25	14	60	12	26	14	65	12	26	13	75	12	36	14	85	12	35	14	100	Postoperative
7.....	12	38	14	83	12	24	13	47	12	27	12	49	11	29	14	64	12	30	13	65	12	33	14	95	Postoperative
8.....	12	38	13	95	11	28	14	60	12	30	13	68	11	32	13	72	12	34	14	80	12	36	13	92	Postoperative
9.....	12	35	14	100	12	26	12	60	11	26	13	50	12	33	14	67	13	35	14	75	12	35	14	85	Postoperative
10.....	12	33	13	85	12	25	13	65	12	28	12	66	12	34	13	73	12	36	13	77	12	33	14	80	Postoperative
11.....	13	30	13	65	12	28	13	56	12	28	14	60	12	32	14	64	12	31	13	64	11	30	13	60	Coronary disease
12.....	12	33	14	69	12	29	14	66	12	34	14	69	12	30	15	68	12	33	14	68	12	36	14	70	Coronary disease
13.....	12	36	13	75	12	32	13	73	13	36	14	74	12	34	14	70	12	35	14	68	12	35	14	68	Coronary disease
14.....	12	32	13	60	12	33	14	61	12	36	14	60	11	28	14	63	12	35	14	64	12	35	14	65	Coronary disease
15.....	12	34	13	61	12	28	14	58	12	30	14	57	12	27	14	59	12	31	15	58	12	29	15	55	Coronary disease
16.....	12	36	14	70	12	32	14	67	12	38	14	73	12	30	15	70	11	29	14	75	12	32	14	72	Thrombophlebitis
17.....	13	32	14	60	13	34	13	64	12	32	14	66	12	32	14	65	12	36	13	66	11	26	14	68	Thrombophlebitis
18.....	12	28	13	56	12	28	13	61	12	30	13	58	12	30	13	56	12	34	13	61	12	28	13	60	Thrombophlebitis
19.....	12	29	14	63	12	27	15	60	11	33	14	62	12	31	14	65	11	30	14	63	13	30	14	65	Thrombophlebitis
20.....	12	26	13	58	12	28	14	62	12	36	13	56	12	30	13	54	12	28	13	58	12	28	13	57	Thrombophlebitis
21.....	11	25	13	50	12	26	14	52	11	32	13	50	13	33	12	55	12	29	13	49	12	27	14	50	Diabetic gangrene
22.....	12	26	12	54	13	28	13	53	12	30	13	55	12	30	13	55	12	28	14	50	12	26	14	56	Diabetic gangrene
23.....	12	26	13	54	12	29	13	58	12	29	14	56	12	29	14	60	12	27	14	53	12	30	14	50	Frostbite gangrene
24.....	12	28	13	58	12	28	14	63	13	28	12	54	12	28	12	52	12	26	14	56	12	31	14	52	Frostbite gangrene
25.....	12	36	14	85	12	35	14	90	12	29	13	93	12	34	13	90	12	35	14	95	12	33	14	95	Normal
26.....	12	34	14	88	12	33	14	97	13	34	14	90	12	38	14	95	12	32	14	89	12	35	14	90	Normal
27.....	12	32	13	99	12	36	14	83	12	35	14	86	12	36	13	99	12	35	14	88	12	35	14	90	Normal
28.....	13	35	13	86	13	38	13	90	12	32	14	95	13	29	14	96	12	33	14	86	12	32	14	92	Normal
29.....	12	35	14	92	12	36	14	95	12	35	14	83	12	38	14	94	12	33	14	84	12	34	14	87	Normal
30.....	12	34	14	95	12	35	14	85	12	35	13	92	12	38	14	96	12	38	14	90	11	36	14	85	Normal

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active substance has, in general, been governed by the minimum clotting time for undiluted normal human plasma. The most widely used source is rabbit brain, and the preparation of greatest activity is acetone-treated rabbit brain tissue. In this connection, special emphasis has been placed on the fact that clotting inhibitors present in brain tissue are removed by treatment with acetone, thereby increasing the activity of the thromboplastic substance.[11]

The difficulty experienced in the preparation of a reagent from acetone-treated rabbit brain to yield a clotting interval of eleven to twelve seconds for normal undiluted plasma has been mentioned in the section on "Material and Methods." The observed decrease in activity was found to be directly associated with the amount of shaking during the incubation period. The factors involved may be resolved into the following possibilities: (1) a denaturing process of the thromboplastic substance, resulting in decreased activity; (2) a more concentrated emulsion, obtained as the consequence of agitation, leading to inhibition of the coagulation reaction,[11] or (3) the liberation of more clotting inhibitors during such treatment. Apparently, little attention has been paid to small variations in clotting time, amounting to two or three seconds. The differences may have been due to technical errors, such as reading of the stopwatch, variations in the thromboplastic content of rabbit brain or variations in prothrombin activity of plasma from normal persons.

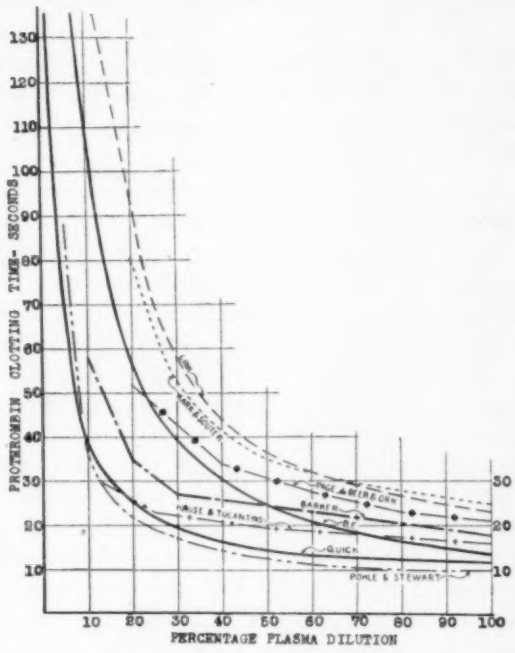

Chart 1.—Comparison of eight prothrombin activity curves of normal human plasma for several types of thromboplastic substance: acetone-treated rabbit brain (Quick,[8] Pohle and Stewart[19] and B. F. [thromboplastic reagent developed during the course of this investigation]); air-dried rabbit brain (Barker,[27b] Link and associates[21] and Souter and Kark[20n]); fresh rabbit brain (Hause and Tocantins[20g]) and snake venom (Page and others[18b]).

Particles of various sizes were observed in the incubated suspension obtained from acetone-treated rabbit brain which was prepared according to Quick's procedure. In the preceding paragraph, the possibility of liberation of clotting inhibitors as the result of agitation suggested that greater uniformity in activity might be attained if the material was ground dry to a fine powder. A saline suspension of the finely divided thromboplastic substance (prepared as described in the section on "Material and Methods") yielded a milky, opaque suspension, in contrast to the translucent supernatant obtained from the unground, desiccated tissue. This preparation contained finely dispersed particles in suspension, which did not readily settle out on standing. The presence of these particles, however, probably does not affect the properties of the reagent.[11] Analysis showed that this emulsion contained one and a half times as much suspended matter as the emulsion prepared by Quick's method. Also, its biologic activity was readily reproduced, as was evidenced by the fact that several hundred preparations from different lots of rabbit brain consistently gave a clotting interval of thirteen to fifteen seconds for undiluted normal plasma and eighty-five to ninety-five seconds for a 12.5 per cent dilution. For these studies, therefore, Quick's thromboplastic reagent has been modified by grinding dry and thorough shaking during the incubation period.

Calcium Chloride Reagent.—Optimum calcium ion concentration is an important factor in the coagulation of decalcified plasma.[19] There is no unanimous agreement with regard to the choice of molarity of the solution of calcium chloride used in the routine determinations of prothrom-

18. (*a*) Fullerton.[20p] (*b*) Page, R. C.; de Beer, E. J., and Orr, M. L.: Prothrombin Studies Using Russell Viper Venom: III. Effect of Lecithinized Venom on Prothrombin Clotting Time, J. Lab. & Clin. Med. **27:** 830, 1942. (*c*) Page and Russell.[20d] (*d*) Shapiro and others.[20m] (*e*) Wright and Prandoni.[20o]

19. (*a*) Quick, A. J.: The Thromboplastin Reagent for the Determination of Prothrombin, Science **92:**113, 1940; (*b*) Calcium Factor in Quantitative Determination of Prothrombin, Proc. Soc. Exper. Biol. & Med. **40:**206, 1939. (*c*) Pohle, F. J., and Stewart, J. K.: A Study of the Quick Method for the Quantitative Determination of Prothrombin with Suggested Modifications, Am. J. M. Sc. **198:**622, 1939.

bin clotting time.[20] Lack of uniformity in this factor may be responsible for some of the discrepancies in the values recorded by various investigators. The strength of calcium chloride solution recommended by Quick in his earlier paper was 0.025 molar.[8] Later, he reported[11] a "more suitable" concentration, i. e., 0.020 molar. Other investigators[19e] have studied the effect of varying calcium ion concentrations on the prothrombin clotting time of undiluted normal plasma. For a given preparation of thromboplastin (Quick) and normal human plasma, Pohle and Stewart[19c] selected a calcium ion concentration which yielded a minimum clotting time, and they obtained a curve manifesting slightly greater activity than Quick's original curve (chart 1). During the course of the present investigation, 0.025 molar solution of calcium chloride was found to be most satisfactory.

20. (*a*) Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3'-Methylenebis (4-Hydroxycoumarin): I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, Am. J. M. Sc. **202**:563, 1941. (*b*) Brambel and Loker.[4] (*c*) Butsch, W. F., and Stewart, J. D.: Administration of Dicoumarin Compound for Prophylaxis and Postoperative Thrombosis and Embolism: A Preliminary Report, Arch. Surg. **45**:551 (Oct.) 1942. (*d*) Page, R. C., and Russell, H. K.: Prothrombin Estimation Using Russell Viper Venom: I. Simple Modification of Quick's Method, J. Lab. & Clin. Med. **26**:1366, 1941. (*e*) Quick (footnotes 8 and 19 *b*). (*f*) Stats, D., and Bullowa, J. G. M.: Effect of a Single Dose of 3,3'-Methylenebis (4-Hydroxycoumarin) upon Blood Coagulation in Humans, Proc. Soc. Exper. Biol. & Med. **50**:66, 1942. (*g*) Hause, W. A., and Tocantins, L. M.: Determinations of Plasma Prothrombin Variations in Normal Men and Women, Am. J. Clin. Path. **11**:54, 1941. (*h*) Lucia, S. P., and Aggeler, P. M.: The Influence of Liver Damage on the Plasma Prothrombin Concentration and the Response to Vitamin K, Am. J. M. Sc. **201**:326, 1941. (*i*) Ziffren, S. E.; Owen, C. A.; Hoffman, G. R., and Smith, H. P.: Control of Vitamin K Therapy: Compensatory Mechanisms of Low Prothrombin Levels, Proc. Soc. Exper. Biol. & Med. **40**:595, 1939. (*j*) Barker.[3c] (*k*) Davidson, C. S., and MacDonald, H.: A Critical Study of the Action of 3,3'-Methylenebis (4-Hydroxycoumarin) (Dicoumarin), Am. J. M. Sc. **205**:24, 1943. (*l*) Magath, T. B.: Technic of Prothrombin Time Determination, Am. J. Clin. Path. (Tech. Supp.) **3**:187, 1939. (*m*) Shapiro, S.; Sherwin, B.; Redish, M., and Campbell, H. A.: Prothrombin Estimation: A Procedure and Clinical Interpretations, Proc. Soc. Exper. Biol. & Med. **50**:85, 1942. (*n*) Souter, A. W., and Kark, R.: Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, Am. J. M. Sc. **200**:603, 1940. (*o*) Wright, I. S., and Prandoni, A.: The Dicoumarin 3,3'-Methylene bis-(4-Hydroxycoumarin): Its Pharmacologic and Therapeutic Action in Man, J. A. M. A. **120**:1015 (Nov. 28) 1942. (*p*) Fullerton, H. W.: Estimation of Prothrombin: A Simplified Method, Lancet **2**:195, 1940.

PROTHROMBIN ACTIVITY CURVES

The clot-activating characteristics of the modified thromboplastic reagent developed during the course of this investigation were studied and compared with those of the reagent prepared and described by Quick.[11] Prothrombin activity curves were constructed, serial dilutions of normal plasma being used. The diluent employed was 0.85 per cent saline solution. Examination of chart 2 shows that different slopes were obtained for the two preparations. A difference of two or three seconds in the clotting interval was encountered for undiluted plasma, but the deviation became progressively greater on dilution. With 12.5 per cent plasma the difference in the clotting interval for the two preparations was fifty-five seconds. Similar observations were reported in an earlier paper,[4] but the factors involved in the discrepancy encountered were not understood until the present detailed study was undertaken.

From the data presented, it becomes apparent that preparations of acetone-treated rabbit brain yielding a clotting interval of eleven to fifteen seconds for undiluted plasma do not give any information concerning the characteristics of the prothrombin activity curve unless other points on the curve are experimentally ascertained. Inspection of the two curves (chart 2) further reveals that the slope of the curve obtained with modified thromboplastic reagent is such that small changes in the relative concentration of prothrombin, that is, the variations obtained by dilution of plasma, correspond to appreciable changes in the clotting interval. On the contrary in Quick's curve large changes in concentration of prothrombin correspond to relatively small changes in the clotting time until after a critical point[8] (hemorrhage level, 20 per cent prothrombin) is attained, when a decided increase in the slope occurs. From this analysis, it is obvious that the modified thromboplastic reagent is more sensitive for detecting variations in prothrombin activity.

The factors responsible for the difference in the characteristics of the slopes of the two prothrombin activity curves (chart 2) may be defined as follows: Dry grinding of the acetone-treated rabbit brain and shaking during the incubation period probably favor the release of clotting inhibitors. Inhibitor substances present in the thromboplastic reagent are of aid in coagulation studies and are not to be considered as undesirable impurities. It seems likely that a satisfactory thromboplastic reagent is one that contains an appropriate balance of prothrombin

activators and inhibitors. By varying the inhibitor content, it is possible to alter Quick's prothrombin activity curve to such an extent that a logarithmic plotting yields a straight line, in which the clotting time is closely proportional to the relative concentration of prothrombin.

The effect of clotting inhibitors on the slope of the prothrombin activity curve was tested in the following manner: A thromboplastic substance containing all the inhibitors was selected,

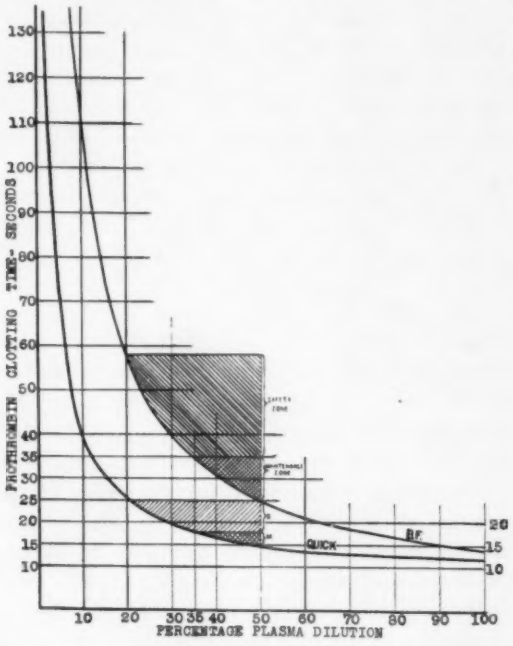

Chart 2.—Comparison of "safety" and "maintenance" zones during administration of dicoumarin for the Quick and the modified (B. F.) thromboplastic reagent. The "safety" zone (hatched area) involves a relative concentration of prothrombin of 35 to 20 per cent (critical hemorrhage level, Quick [8]) of normal: For B. F. reagent the clotting range is twenty-five seconds, and for the Quick reagent (designated S), seven seconds. The "manitenance" zone (cross-hatched area) involves a relative concentration of prothrombin of 50 to 35 per cent of normal: For B. F. reagent the range of clotting times is ten seconds, and for the Quick reagent (designated M) it is three seconds.

that is, one in which acetone was not used in the process of preparation. The product was prepared by drying it in a vacuum desiccator containing calcium chloride.[21] A saline suspension of this material was prepared in the same manner as described before (see section "Material and Methods"), and determinations of prothrombin clotting time were made, using serial dilutions of normal human plasma. A sample of the vacuum-desiccated product was then extracted with large volumes of acetone and again tested in the same manner. The prothrombin activity curves obtained with these two preparations are shown in chart 3. After extraction with acetone a pronounced change in slope and a definite increase in activity were noted. The same chart (chart 3) also shows the effect of reextraction on acetone-treated rabbit brain which has been ground dry, demonstrating a decrease in slope as well as an increase in activity approximating Quick's curve.

Three commercial brands of thromboplastic substance were examined in a similar manner. The prothrombin activity curves obtained revealed that inhibitor substances were reduced to a minimum in them. By virtue of this fact, such preparations possess optimum activity and good reproducibility but decreased sensitivity.

In view of the evidence just presented, it is apparent that two types of thromboplastic substance are now available for studies of the pro-

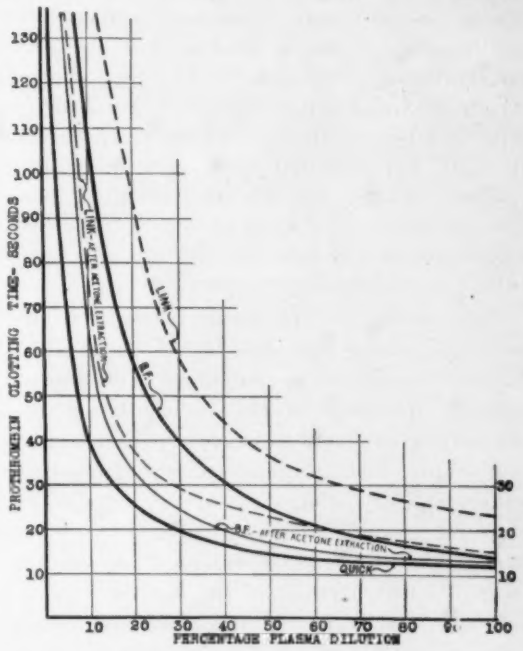

Chart 3.—Effect of extraction with acetone on the activity of thromboplastic substance. The Link [21] and the modified (B. F.) preparation are compared. Link's preparation shows the greatest increase in activity after extraction with acetone. The B. F. preparation shows decided increase in activity when the relative concentration of prothrombin is decreased. After extraction with acetone the prothrombin activity curves of the two preparations approach those of Quick's. Normal human plasma was used to construct these curves. This chart shows that acetone removes inhibitor substances from rabbit brain tissue.

21. Campbell, H. A.; Smith, W. K.; Roberts, W. L., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: II. The Bioassay of Hemorrhagic Concentrates by Following the Prothrombin Level in the Plasma of Rabbit Blood, J. Biol. Chem. **138**:1, 1941.

thrombin clotting time by the Quick method. One contains a certain balance of activators and inhibitors, while the other contains a predominance of activators and a minimum of inhibitors. The choice reagent depends on factors determining clinical applicability; that is, the reagent with which the coagulation mechanism is best demonstrated should be employed. Each type can be reproduced as desired.

PROTHROMBIN INHIBITORS AS AGENTS FOR DETECTING A TENDENCY TO INTRAVASCULAR CLOTTING

It is generally known that in certain clinical conditions increased coagulability of plasma occurs, with resulting intravascular disorders.[22] If such enhanced clotting activity is the consequence of an increase in prothrombin activators, an inhibitor present in the thromboplastic reagent should provide a means of detecting them. In tests, the excess activator present would neutralize or counteract the inhibitor, and a lower prothrombin clotting time than normal should result. Such differences in clotting activity in normal and in pathogenic states cannot be demonstrated in undiluted plasma. They are detectable only on dilution, and the selected concentration of plasma is 12.5 per cent with which maximal differences have been obtained. The shortness of the clotting interval, the limitations of experimental error and other factors militate against the use of undiluted plasma. The sensitivity of diluted plasma with respect to variations in prothrombin activity has already been reported in the literature.[23]

The validity of the thesis formulated in the preceding paragraph was tested on a series of patients with diverse pathologic conditions involving disorders in blood coagulation (postoperative complications, coronary disease, thrombophlebitis, diabetic gangrene and gangrene resulting from frostbite), as well as on a series of clinically normal persons (table 1). The patients were selected at random and were not treated with dicoumarin during the period of testing. Two types of thromboplastic reagent, Quick's and the modified preparation (B. F.), were used. Undiluted and 12.5 per cent plasma were compared for each person for each test period with both types of thromboplastic reagent. With undiluted plasma no significant variation was observed at any time for any of the different categories of patients with Quick's reagent or with the modified preparation. Examination of the results obtained with 12.5 per cent plasma reveals great diversities which may form the basis for classification. The data obtained on patients with the aforementioned clinical conditions indicate a decreased clotting interval, which may be interpreted as increased coagulability of plasma. Also, the difference in clotting intervals for dilute plasma and for "normal" plasma was greater when the modified thromboplastic reagent was used, indicating more delicate sensitivity. The subjects in the postoperative group manifested a transient period (six or seven days) of hypercoagulability. Thrombotic complications are likely to occur and have been observed in patients for whom this period has been prolonged, with a clotting interval of forty-five to sixty-five seconds for 12.5 per cent plasma. The patients comprising the other four groups consistently showed a clotting interval of fifty to seventy seconds with the same dilution. The results presented in table 1 demonstrate the clinical applicability of the modified thromboplastic reagent.

The data obtained through the use of inhibitor substances in the thromboplastic reagent capable of detecting a tendency to intravascular clotting correspond with those obtained by de Takáts [5a] with his technic for testing tolerance to heparin. With both procedures one may apparently evaluate the relative existence of substances that are responsible for hypercoagulability of blood, correlated usually with disturbances of the peripheral vascular system.

STUDIES ON DICOUMARIN

Dicoumarin therapy maintains induced hypoprothrombinemia without hemorrhagic complications. Among the difficulties encountered with use of this type of in vivo anticoagulant, the following phenomena merit special mention: (1) an unusual response after the initial dose, or a "hyperreaction," and (2) an unpredictable response during the course of administration, after an established prothrombin activity level has been maintained in the patient. Technically, the most important problems associated with administration of dicoumarin are as follows: establishment of a margin of safety with respect to hemorrhagic manifestations before they are clinically apparent and interpolation of the results obtained by various procedures and workers. The critical level of prothrombin activity at which bleeding is likely to occur has been defined as 15 to 20 per cent of normal.[8] The efficacious therapeutic clotting time level or the decreased percentage of

22. (*a*) de Takáts.[1c] (*b*) Homans.[1f]

23. Fullerton.[20p] Campbell and others.[21] Brambel and Loker.[9] Sturm, E.: The Prothrombin Concentration in the Plasma of Normal and Leukemic Rats, Cancer Research **4**:35, 1944. Shapiro and others.[20m]

prothrombin to be maintained during administration of dicoumarin has yet to be generally established. For practical purposes, there should be a "maintenance zone," in which the patient could be kept with little difficulty, and a "safety zone," to take care of unusual responses without the possibility of hemorrhagic complications.

The characteristics of two types of thromboplastic preparation (Quick's and the B. F. reagent) were compared in an effort to ascertain which was more suitable for use after administration of dicoumarin. Fifteen patients who had been treated with varying doses of dicoumarin were selected at random and were studied during five successive testing periods, using both preparations. Forty-eight hours elapsed between each two test periods. The data so obtained are assembled in table 2. Two types of computation of the percentage of prothrombin are also included: namely, an index (ratio of the clotting interval of normal plasma to the clotting interval of plasma treated with dicoumarin) and percentage of prothrombin (the value read from the corresponding activity curve, given the clotting interval).

Inspection of the data presented in table 2 reveals that the values for activity curves for the two thromboplastic preparations studied (chart 2) can be interpolated. If the clotting interval is determined for the modified reagent, the corresponding time can be predicted for Quick's reagent, and vice versa, through a wide range of values. The tabulated figures in some instances deviate slightly from the graphic estimations. The relative percentage of prothrombin obtained as the index is within 8 per cent of the concentration read from the prothrombin activity curve obtained with the modified reagent. However, when the curve obtained with Quick's reagent is used, the percentage difference is greatly increased, demonstrating the unreliability of the index, to be explained later.

Throughout the entire course of clinical investigation of dicoumarin at Mercy Hospital, the choice of a maintenance prothrombin activity level was twenty-five to thirty-five seconds (relative concentration of prothrombin of 35 to 50 per cent) for undiluted plasma. The vast majority (96 per cent) of patients treated showed no signs of hemorrhagic manifestations or thrombotic complications. It was felt that the danger of untoward reactions would be minimized, in view of the degree of sensitivity of the prothrombin activity curve (B. F.). A margin of an additional twenty-five seconds was allowed before the critical level was attained. In chart 2 the activity curves are compared with respect to the choice of a "maintenance zone" and a "safety zone" for patients treated with dicoumarin. For the same degree of decrease in prothrombin activity the modified preparation gives greater sensitivity than does Quick's preparation. It should be mentioned at this point that some workers treat patients with dicoumarin when the prothrombin concentration is at or near the critical level, i. e., 10 to 30 per cent prothrombin, with satisfactory clinical results, but bleeding in a greater percentage of patients [3c] (about 8 per cent).

An unpredictable increase in response during the course of administration of dicoumarin is sometimes encountered after the patient has apparently been maintained on an established prothrombin activity level. Such instances, fortunately, have been rare. Some of the factors responsible for the unpredictable response are: increased atmospheric temperature,[24] elevation in the patient's temperature and sudden change in the patient's condition. Such circumstances indicate the importance of allowing a wide margin of safety in the selection of a maintenance level of prothrombin activity and of being able to detect sudden changes before the onset of serious consequences.

METHODS OF RECORDING LABORATORY FINDINGS

The interpretation and correlation of the evidence in the current literature on administration of dicoumarin is a difficult task at present because of the lack of uniformity for reporting laboratory findings. Three methods of recording results are in use: (1) prothrombin clotting time of plasma, expressed in seconds [25]; (2) percentage of prothrombin obtained from the ratio of the clotting time of normal plasma to that of plasma treated with dicoumarin,[26] and (3) percentage of prothrombin obtained from normal plasma dilution curves.[27] A comparison has been made of two thromboplastic preparations (Quick's and the B. F. reagent) and the data are assembled in table 2. It is my purpose to discuss briefly the relative merits of each one.

24. Richards, R. K.: Influence of Fever upon the Action of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) (Dicoumarol), Science **97**:313, 1943.

25. Quick.[8] Brambel and Loker.[6a] Page and others (footnotes 20 *d* and 18 *b*). Pohle and Stewart.[19e] Barker.[3c] Souter and Kark.[20n] Hause and Tocantins.[20g] Wright and Prandoni.[20o] Magath.[20l] Ziffren and others.[20l] Allen, E. V.; Barker, N. W., and Waugh, J. M.: A Preparation from Spoiled Sweet Clover [3,3'-Methylene-Bis-(Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood: A Clinical Study, J. A. M. A. **120**:1009 (Nov. 28) 1942.

(Footnotes continued on next page)

1. *Prothrombin Clotting Time of Plasma Expressed in Seconds.*[25]—This form of expression is most generally used. It has the advantage of presenting primary data as obtained in the laboratory without mathematical embellishments. However, different values for normal undiluted plasma have been reported from various institutions, depending on the type of thromboplastic preparation used in the test. The curves presented in chart 1 demonstrate the difficulties encountered. But in the preceding sections the necessity for ascertaining the clotting interval of various dilutions of normal plasma has been stressed as a means of standardization of the thromboplastic reagent. In this manner, undue variations in the values for plasma which has been treated with dicoumarin for any given procedure would be minimized. Thus, a therapeutic range in the clotting interval could be established for each modification, e. g., twenty-five to thirty-five seconds, as used at Mercy Hospital (chart 2) or twenty-seven to sixty seconds, as used at the Mayo Clinic. The interpretation of such differences in the range of coagulation time used in dicoumarin therapy becomes perplexing.

During the course of the present investigation, two thromboplastic preparations were studied in parallel, with the result that from available prothrombin activity curves and the clotting interval for one preparation, the clotting interval for the other preparation could be obtained graphically (table 2; chart 2). In the same manner, the values for all other types of thromboplastic substances could be interpolated, although such parallel data are not available at present.

2. *Percentage of Prothrombin Obtained from Ratio of the Clotting Time of Normal Plasma to the Clotting Time of Plasma Treated with Dicoumarin.*[26]—Such an expression is only an index of the clotting time and bears a relationship to prothrombin activity only if the plasma dilution curve is a logarithmic straight line (the logarithm of the clotting time plotted against the logarithm of the relative concentration of prothrombin). The data in table 2 reveal that with the modified preparation a closely approximate proportionality exists but that with Quick's preparation distinct deviations occur. These findings illustrate the applicability of prothrombin inhibitors in the preparation of a suitable activity curve. Attempts at interpolation of the reported findings have been difficult, since this index does not take into consideration such factors as the clot-activating properties of the thromboplastic reagent.

3. *Percentage of Prothrombin Obtained from Normal Plasma Dilution Curves.*[27]—If activity curves are constructed from serial dilutions of normal plasma, the percentage of prothrombin

TABLE 2.—*Sensitivity of the Quick and the Modified Thromboplastic Reagent*

	Thromboplastin								Thromboplastin								Thrombo			
	Quick				B. F.				Quick				B. F.				Quick			
	Per Cent Prothrombin		Plasma Clotting Time, Sec.		Per Cent Prothrombin		Plasma Clotting Time, Sec.		Per Cent Prothrombin		Plasma Clotting Time, Sec.		Per Cent Prothrombin		Plasma Clotting Time, Sec.		Per Cent Prothrombin		Plasma Clotting Time, Sec.	
	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %
1	80	49	15	57	57	51	24	405	80	49	15	58	64	56	22	380	75	44	16	55
2	86	54	14	37	52	59	21	210	86	55	14	54	67	59	21	371	100	100	12	35
3	75	44	16	54	70	63	20	365	71	38	17	74	54	48	29	400	63	31	19	76
4	100	100	12	29	93	90	15	76	100	100	12	34	82	77	17	193	86	55	14	60
5	100	100	12	27	100	100	14	63	81	55	14	46	82	77	17	108	86	55	14	51
6	109	100	11	26	108	100	13	63	52	23	23	55	35	30	40	400	100	100	12	42
7	57	27	21	120	33	28	42	400	80	49	15	50	67	54	21	400	67	34	18	112
8	80	48	15	56	54	48	26	397	71	38	17	82	44	38	32	400	63	31	19	70
9	100	100	12	45	87	85	16	112	80	48	15	56	54	48	26	398	75	44	16	64
10	100	100	12	29	100	100	13	60	92	70	13	45	74	67	19	220	86	54	14	46
11	80	48	15	64	64	57	22	310	73	44	16	71	50	44	28	400	71	38	17	73
12	80	48	15	52	56	50	25	360	86	54	14	56	51	50	25	378	67	34	18	80
13	86	54	14	50	70	63	20	380	65	31	19	79	33	28	42	400	86	54	14	55
14	92	70	13	48	83	79	17	130	80	48	15	62	64	57	22	320	80	48	15	64
15	100	100	11	34	88	85	16	98	86	54	14	55	83	79	17	249	67	34	18	126

26. Evans, J. A.: Problems of Postoperative Thrombophlebitis and Pulmonary Embolism, Connecticut M. J. **8**:71, 1944. Wasserman, L. R., and Stats, D.: Clinical Observations on the Effect of 3,3'-Methylenebis (4-Hydroxycoumarin), Am. J. M. Sc. **206**:466, 1943. Cahan.[3a] Zucker, H. D.: Clinical Experiences with Dicoumarol, J. A. M. A. **124**:217 (Jan. 22) 1944. Evans, J. A.: Dicoumarol Therapy in Thrombotic Emergencies, New England J. Med. **230**:131, 1944.

27. (*a*) Davidson and Mac Donald.[20k] (*b*) Barker, N. W.: Personal communication to the author.

for plasma which has been treated with dicoumarin can be ascertained with a reasonable degree of accuracy. Standardization and duplication of the clotting interval for dilutions of plasma ranging from 50 per cent downward are essential, because the coagulation rate during treatment with dicoumarin falls in this zone. Inspection of the data in table 2 shows that close agreement of the percentage of prothrombin can be obtained with two thromboplastic preparations if the value is graphically read from the corresponding curve. This evidence indicates that determination of the relative percentage of prothrombin is possible within reasonable limits of experimental error, regardless of the characteristics of the prothrombin activity curves, and that therefore it is the method of choice for reporting laboratory findings in the literature.

tolerance technic.[3a] This thromboplastic reagent is easily prepared and reproduced.

The present investigation shows that the presence of inhibitors in the thromboplastic reagent results in an increased sensitivity of the prothrombin activity curve. For use after the administration of dicoumarin, a desirable activity curve is one in which the slope is such that small changes in prothrombin activity can be detected. For detection of such changes Quick's thromboplastic emulsion is not entirely satisfactory. A curve is obtained in which large changes in prothrombin activity correspond to small variations in the clotting interval until a critical level is reached. This point corresponds to prothrombin activity of 15 to 20 per cent. The modified

in Determination of Percentage of Prothrombin and the Plasma Clotting Time

plastin				Thromboplastin								Thromboplastin							
B. F.				Quick				B. F.				Quick				B. F.			
Per Cent Prothrombin		Plasma Clotting Time, Sec.		Per Cent Prothrombin		Plasma Clotting Time, Sec.		Per Cent Prothrombin		Plasma Clotting Time, Sec.		Per Cent Prothrombin		Plasma Clotting Time, Sec.		Per Cent Prothrombin		Plasma Clotting Time, Sec.	
Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %
54	48	26	398	67	34	18	80	41	36	34	400	67	34	18	83	38	33	37	400
100	100	14	123	100	100	12	40	67	60	21	166	80	49	15	67	58	51	24	353
40	34	35	400	67	34	18	70	37	38	32	400	80	49	15	66	52	45	27	400
47	41	30	400	71	39	17	68	64	57	22	230	80	49	15	64	51	50	25	390
61	55	23	334	86	54	14	50	48	42	29	400	63	31	19	80	50	43	28	400
74	66	19	280	80	49	15	55	47	41	30	400	71	39	17	70	51	50	25	400
45	40	31	400	60	29	20	120	33	27	43	400	63	31	19	74	44	38	32	400
37	32	38	400	71	38	17	76	41	36	34	400	50	22	24	100	26	21	54	400
47	41	30	400	41	16	29	136	20	16	70	400	43	17	28	112	22	18	66	400
61	54	23	220	92	70	13	32	56	50	25	392	86	54	14	80	61	54	23	390
44	38	32	400	57	26	21	128	32	27	44	400	46	19	26	106	24	20	58	400
39	33	36	400	44	18	27	115	22	18	64	400	33	11	36	152	15	12	94	400
67	59	21	400	71	38	17	60	38	33	37	400	75	44	16	74	48	42	29	400
47	41	30	400	50	22	24	112	27	22	52	400	37	14	32	141	17	14	80	400
37	32	38	400	80	48	15	25	38	33	36	400	80	48	15	80	54	48	26	400

SUMMARY

With a modification of the thromboplastic reagent used in Quick's one stage procedure for determining prothrombin clotting time, coagulation rates deviating from normal can be detected with 12.5 per cent plasma. Undiluted plasma is not satisfactory for this purpose because of the shortness of the clotting interval. Increased clotting rates have been demonstrated by this method for the following clinical conditions: thrombophlebitis, coronary thrombosis, postoperative trauma and gangrene (frostbite and arteriosclerosis). The results so obtained correspond to the findings with de Takáts' heparin thromboplastic reagent developed during the course of this study possesses the desired properties; that is, for small changes in prothrombin activity a pronounced change in the clotting interval is obtained. The use of such a preparation should greatly minimize the hazards encountered during this type of anticoagulant therapy.

The determination of the percentage of prothrombin from prothrombin activity curves obtained by serial dilution of normal human plasma is recommended. In this manner, uniformity in recording laboratory findings, as well as the definition of a therapeutic prothrombin activity level to be maintained during the course of administration of dicoumarin, could be achieved, which would not be affected by modifications in the procedure.

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TRANSPLANTATION OF EPIPHYSIAL CARTILAGE

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Many experiments concerned with the transplantation of epiphysial cartilage have been performed in the past, with varying amounts of success. Helferich,[1] Rehn and Wakabayashi,[2] von Tappeiner,[3] Obata[4] and Heller[5] all reported some degree of subsequent longitudinal growth of bone. Heller, especially, had remarkably good results in 120 experiments and concluded that autoplastic reimplantation of the epiphysial plate was successful and that the procedure offered a promise of favorable application in man. Fohl,[6] working with an epiphysial cartilage plate and a piece of attached diaphysis, likewise expressed the belief that the results justified practical clinical application.

Haas,[7] on the other hand, has been antagonistic to the procedure on the ground that the epiphysial cartilage plate loses its power of causing growth of bone after transplantation and that one is not warranted in attempting such a transplantation in a patient with the expectation of obtaining longitudinal growth of bone. Bisgard[8] similarly decried clinical application of this surgical procedure, because of the "magnitude of the operation and the uncertainty of the results."

The only successful transplantation performed on a human being was that reported by Straub.[9] In 1912 he transplanted a piece of diaphysis with the epiphysial line and a part of the epiphysis in a child 6½ years of age. A follow-up record made seventeen years later (1929) showed that the epiphysis had survived, grown and continued to function physiologically. Haas challenged this statement and claimed that no longitudinal growth of bone had taken place.

However, the encouraging reports of the earlier workers, the theoretic soundness of the procedure and the tremendous benefits to be derived from a successful operation make even an attempt at transplantation justifiable. Accordingly, in 1941 I transplanted in a child of 7 years the epiphysis of the fibula and part of the attached diaphysis to this first metatarsal bone, which had been almost completely destroyed.

This paper is a report of this unusual operation and the satisfactory results obtained to date. The patient has been observed postoperatively for only four years, and, since he is still growing, the eventual fate of the transplant is, of course, not known. However, the gratifying improvement up to the time of writing and the relative ease of operative technic (it should be within the scope of any well trained orthopedic specialist) have convinced me that it is a valuable procedure and should be attempted on young children when epiphysial centers have been destroyed and growth of bone is desired.

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2. Rehn, E., and Wakabayashi: Die homoplastische Transplantation des Intermediärknorpels im Tierexperiment, Arch. f. klin. Chir. **97**:1, 1912.

3. von Tappeiner, F.: Studien zur Frage der Transplantationsfähigheit des Epiphysenknörpels und des Gelenkknörpels, Ztschr. f. d. ges. exper. Med. **1**:491, 1913.

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6. Fohl, T.: Versuche über die Transplantation der Knörpelfuge, Arch. f. klin. Chir. **155**:232, 1929.

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8. Bisgard, J. D.: Transplanted Epiphysial Cartilage, Arch. Surg. **39**:1028 (Dec.) 1939.

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REPORT OF A CASE

D. R., an 11 year old white boy, was injured in 1937 (at the age of 3 years), when some one stepped on his left foot with a hard, sharp high heel. Two days after this accident cellulitis of the foot developed. The condition grew progressively worse, and an operation was performed, which revealed osteomyelitis of the first metatarsal bone. In spite of the use of wet dressings and the usual postoperative treatment, the patient did badly, and because of his desperate condition amputation of the foot was contemplated. It was at this time (1937) that the child came under my care. Physical examination showed that the boy was acutely ill with a temperature of 103 F. Significant findings were limited to the left foot, which was swollen and edematous, with the swelling involving half of the left leg above the ankle. There

Fig. 1.—Roentgenogram taken shortly after the patient (aged 3 years), was injured, when some one stepped on his left foot, reveals total destruction and dissolution of the first metatarsal bone of the left foot, due to osteomyelitis.

was a draining sinus in the region of the first metatarsal bone.

A roentgenogram (fig. 1), taken on March 22, 1937, showed complete destruction and dissolution of the first metatarsal bone.

The Orr treatment for pyogenic osteomyelitis was immediately instituted, and the patient rallied slowly. The local soft tissue completely healed, and there was some attempt at regeneration of bone. This, however, was incomplete, and the result was extreme shortening of the large toe, with considerable pronation of the foot. Metal arch supports were made to keep the foot in the proper position, but the deformity became worse and operation was indicated. Therefore, on Jan. 28, 1941, approximately four years after the injury, transplantation of the epiphysis of the opposite fibular head was performed, with the following technic.

A 6 inch (15 cm.) incision was made over the lateral aspect of the right knee, and the peroneal nerve was isolated. Adhesive tape was placed around the nerve, and the nerve was followed until all of its terminal branches were found. The head of the fibula and a portion of the shaft, the total section measuring about 2 inches (5 cm.), were resected with an osteotome and a chisel. The wound was then closed, no. 1 plain surgical gut being used for the fascia and muscle and black silk for the skin.

Fig. 2.—*A*, roentgenogram of the left foot taken before operation shows appreciable regeneration of the first metatarsal bone (fig. 1) but considerable shortening of the shaft and fragmentation of the proximal portion. *B*, imprint of both feet, made before operation. The toes of the right foot are in normal position. In contrast, the large toe of the left foot is much smaller, and the normal relationship is lost.

A 4 inch (10 cm.) incision was then made on the dorsum of the left foot over the first metatarsal bone, exposing the bone. The shaft of the metatarsal bone was greatly shortened, and the proximal portion was fragmented. This fragmented bone was removed, a small distal section of the healthy bone being left. Forward

traction was then exerted on the great toe, and the epiphysial transplant, including a section of diaphysis from the fibula (which had been trimmed down to 7/8 inch [2 cm.]), was wedged into the space between the distal portion of the metatarsal bone, on one end, and the cuneiform bone, on the other. Throughout the manipulation the bone transplant from the upper end of the fibula was kept scrupulously intact, as far as the epiphysial junction with the metaphysis was concerned. When traction on the great toe was released, the transplant was under sufficient tension to maintain an adequate position, and the toe was appreciably lengthened. The fascia was closed with no. 1 plain surgical gut, and the skin was approximated with silk. A circular plaster cast was applied from the toes to a point above the knee and was left in place for about four weeks.

Recovery was uneventful. When all tenderness of the foot had disappeared, after removal of the cast, the child was permitted to walk with the aid of an orthopedic shoe and a Whitman metal plate. A roentgenogram (taken Feb. 14, 1941) showed the transplant in situ. This film further showed that the first metatarsal bone of the foot which had been operated on was of the same length as the corresponding bone in the opposite foot. The combined length of the metatarsal and the cuneiform bone was ⅛ inch (0.3 cm.) shorter on the side of operation.

Fig. 3.—Roentgenogram taken approximately two weeks after operation shows that the previously fragmented proximal portion of the first metatarsal bone of the left foot has been removed and that the epiphysial transplant from the opposite fibula, with a small segment of attached diaphysis, is now in situ. The transplant has restored the length of the metatarsal bone, which is now of the same size as that in the normal foot (figs. 1 and 2 *A* and table).

The child was observed for over two years and was clinically in excellent condition. His gait was normal, and he participated in all activities, with no complaints. There was moderate pronation of the foot, which was corrected by an ordinary Whitman arch.

The child recently moved to the Midwest and has been observed by Dr. Frederick C. Kidner, of Detroit, for the past year. A recent roentgenogram (taken on Sept. 2, 1944 and obtained from Dr. Kidner) revealed an increase in length as well as width of the metatarsal bone. The length of this bone is exactly the same as that of the metatarsal in the normal foot. Measurements made shortly after the operation and approximately four years later are given in the table.

Fig. 4.—*A*, roentgenogram of the feet taken two years after operation reveals that the first metatarsal bones have grown and are of exactly the same size. *B*, photograph of both feet taken at the same time as the roentgenogram in *A* shows a practically normal-appearing large toe on the left foot, which is slightly shorter than the corresponding member on the right foot.

COMMENT

At the time of writing the proximal portion of the epiphysis had lost its anatomic distinctness and appeared to be fused with the cuneiform bone. However, the size of the metatarsal bone which had been operated on had kept pace with the corresponding member on the opposite side.

From this it must be concluded that up to the present the osteogenic properties of the transplant have not been impaired. This is to be expected, since longitudinal growth of bone takes place at the distal end of the epiphysis, at the epiphysial plate and at the proximal end of the diaphysis; fusion of the proximal part of the epiphysis with the cuneiform bone should, therefore, not interfere with growth of the bone.

Why arthrodesis took place in spite of cartilaginous tissue on the epiphysis and the cuneiform bone and a fibrous capsule is interesting, as well as important. Generally fusion is dependent on the presence of raw bone surfaces. A tenable explanation may lie in the degree of tension existing between the two bones, the cuneiform and the transplant, after traction on the toe was released. If the entire transplant becomes solidly fused and longitudinal growth of bone is arrested, tension may then be a factor, but it does not appear to be vital at the moment.

Fig. 5.—A roentgenogram taken about four years after operation reveals definite evidence of growth of the first metatarsal bone of the left foot as a result of the transplanted epiphysial cartilage. The measurements of the metatarsal bones in the two feet are identical (table). The proximal portion of the transplant appears to have fused with the cuneiform bone, but longitudinal growth of the metatarsal bone is relatively unimpaired to date.

Measurements of the First Metatarsal and the Cuneiform Bones

	Left Foot	Right Foot	Comments
Date: Feb. 14, 1941 (approximately two weeks after operation)			
Graft.....	7/8 inch (3 cm.)		
Metatarsal bone	1 13/16 inches (4.6 cm.)	1 13/16 inches (4.6 cm.)	Right and left first metatarsal bones of exactly the same size
Metatarsal bone plus cuneiform bone	2 1/2 inches (6 cm.)	2 5/8 inches (6.7 cm.)	Normal cuneiform and first metatarsal bones of right foot 1/8 inch (0.3 cm.) longer than corresponding bones on opposite side
Date: September 1944			
Graft.....	1 3/8 inches (3.5 cm.)	.....	Graft has grown 1/2 inch (1.2 cm.) since Feb. 14, 1941
Metatarsal bone	2 3/8 inches (6 cm.)	2 3/8 inches (6 cm.)	First metatarsal bones exactly the same size in the two feet
Metatarsal bone plus cuneiform bone	3 3/16 inches (8.1 cm.)	3 7/16 inches (8.7 cm.)	Cuneiform and first metatarsal bones of right foot 1/4 inch (0.64 cm.) longer than corresponding bones on opposite side

SUMMARY AND CONCLUSION

Epiphysial cartilage from a fibula, containing a portion of diaphysis, was successfully transplanted to the first metatarsal bone.

The toe, which was greatly shortened prior to operation, was immediately corrected by the transplant.

Observations made over approximately three years show that the transplant has "taken" and is functioning physiologically.

The metatarsal bone in the foot which was operated on is of exactly the same size as the bone in the opposite foot.

The proximal portion of the epiphysis appears to have fused with the cuneiform bone without impairing the growth of bone, which takes place more distally.

The eventual fate of the transplant cannot be prophesied at this time, but the extremely gratifying results obtained to date give assurance that this procedure is valuable.

44 Gramercy Park North.

BLOCKING OF THE MIDDLE CERVICAL AND STELLATE GANGLIONS WITH DESCENDING INFILTRATION ANESTHESIA

TECHNIC, ACCIDENTS AND THERAPEUTIC INDICATIONS

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The progress made recently in the diagnosis and treatment of certain diseases dependent on, or influenced by, stellate ganglion innervation has led to the current practice of blocking this ganglion by the infiltration of procaine hydrochloride.

Although therapeutic indications for this practice are numerous today, the procedure has not been sufficiently popularized among surgeons who are interested in the therapeutic results obtainable from acting on the sympathetic innervation. The principal reason for this lack of popularity is the technical difficulty of blocking the stellate ganglion without accident and in such a way as to be well tolerated by the patient, particularly when repeated blocking with an anesthetic is necessary.

This difficulty has been recognized by all with experience in blocking the stellate ganglion with an anesthetic. The problem results from the deep location of this ganglion and from its close relations to important organs. Owing to the anatomic relations of the ganglion, precise infiltration is difficult (Wertheimer and Trillat[1]). Lambret, Razemon and Decoulx[2] affirmed that infiltration of the stellate ganglion with an anesthetic is a painstaking procedure, whether the anterior, lateral or posterior approach is used.

During the decade since 1934 I have had the opportunity of blocking the stellate ganglion in several hundred cases of the most varied conditions. At first, during the time (1934-1936) in which I worked with Professor Leriche, in Strasbourg, I followed the technic recommended by him and Fontaine.[3] Then I tried the technics proposed by Arnulf,[4] Goinard (cited by Lambret and associates[2]), Mandl,[5] White and co-workers[6] and Wertheimer and Trillat[1] before I decided on the method which I have employed consistently during the last five years; experience with numerous cases has demonstrated that this method is free from hazards, is well tolerated by the patient and is uniformly successful.

I began my investigations by studying the causes of accidents and the difficulties encountered with the technics already known. In all methods of approach to the stellate ganglion until now described, the tip of the needle was always carried close to the ganglion. However, anatomic study of the relations of this ganglion to the vertebral and subclavian arteries and to the pleural cupula showed that these structures may be wounded frequently when the needle is introduced so as to attain direct contact with the stellate ganglion, whether the approach used is anterior or lateral.

This observation led me to search for a point of osseous reference in the deep plane, easy of identification by palpation through the soft tissues, to which the tip of the needle could be directed in order to avoid perforation of the vessels and of the pleural cupula. After a study

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1. Wertheimer, P., and Trillat, A.: L'infiltration anesthésique de la chaine thoracique: Technique et résultats, Presse méd. **44**:1356, 1936.

2. Lambret, O.; Razemon, P., and Decoulx, P.: Technique de la chirurgie du sympathique et de ses infiltrations, Paris, Gaston Doin & Cie, 1939.

3. Leriche, R., and Fontaine, R.: L'anesthésie isolée du ganglion étoilé: Sa technique, ses indications, ses résultats, Presse méd. **42**:849, 1934.

4. Arnulf, G.: Infiltration du ganglion stellaire et de la chaine thoracique supérieure par voie supéro-externe, Presse méd. **46**:1726, 1938.

5. Mandl, F.: Die Wirkung der paravertebralen Injektion bei Angina pectoris, Arch. f. klin. Chir. **136**: 495, 1925.

6. (*a*) White, J. C., and White, P. D.: Angina Pectoris: Treatment with Paravertebral Alcohol Injection, J. A. M. A. **90**:1099 (April 7) 1928. (*b*) White, J. C.; Garrey, W. E., and Atkins, J. A.: Cardiac Innervation: Experimental and Clinical Studies, Arch. Surg. **26**:765 (May) 1933. (*c*) White, J. C.: Diagnostic Blocking of Sympathetic Nerves to the Extremities with Procaine, J. A. M. A. **94**:1382 (May 3) 1930; (*d*) Experimental and Clinical Studies in the Surgical Treatment of Angina Pectoris, Ann. Int. Med. **7**:229, 1933; (*e*) Technique of Paravertebral Alcohol Injection: Methods and Safeguards in Its Use in the Treatment of Angina Pectoris, Surg., Gynec. & Obst. **71**:334, 1940. (*f*) White, J. C., and Smithwick, R. H.: The Autonomic Nervous System: Anatomy, Physiology and Surgical Application, ed. 2, New York, The Macmillan Company, 1941.

of the topographic relations of the middle sympathetic cervical and the stellate ganglion to the skeleton, the transverse process of the sixth cervical vertebra was taken as the deep point of osseous reference.

Furthermore, study of the morphology and of the normal and pathologic physiology of the cervical and the thoracic portion of the sympathetic trunk convinced me that in order to obtain the most intense vasomotor effect in the upper extremity and in the thorax, it is not enough to anesthetize the stellate ganglion only. It is necessary to anesthetize also the intermediate ganglion, which is located above the stellate ganglion and near the vertebral artery, and the

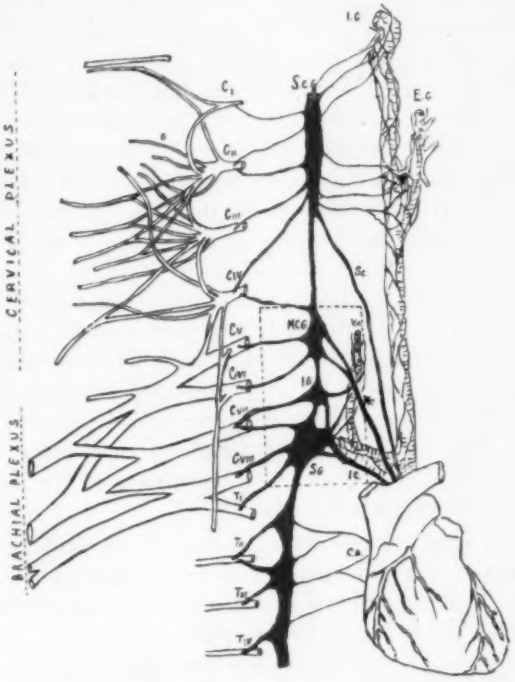

Fig. 1.—The three cervical sympathetic ganglions (middle cervical, intermediate and stellate), from which arise the communicating branches for the brachial plexus, the branches for the vertebral nerve and the two cardiac nerves (middle and inferior). *S.C.G.* indicates superior cervical ganglion; *M.C.G.*, middle cervical ganglion; *I.G.*, intermediate ganglion; *S.G.*, stellate ganglion; *S.C.*, superior cervical cardiac nerve; *M.C.*, middle cervical cardiac nerve; *I.C.*, inferior cervical cardiac nerve; *C.B.*, sympathetic cardiac branches.

middle cervical sympathetic ganglion, which is normally located at the level of the sixth cervical vertebra.

The middle cervical, intermediate and stellate ganglions constitute an anatomic and physiologic group (fig. 1), which has under its control the vasomotor innervation and the sensory sympathetic pathways of the upper extremity and of the heart, as well as certain portions of the distribution to the organs of the neck, face and cranium. The communicating branches to the fifth and sixth trunks of the brachial plexus arise from the middle cervical ganglion (Gray[7]; Cunningham[8]), and those to the seventh and eighth cervical trunks, from the intermediate and stellate ganglions (Huber[9]; Morris[10]). The heart receives, besides the inferior cardiac nerve, which arises from the stellate ganglion, a middle cardiac nerve, originating from the middle cervical ganglion, the largest of the three cardiac nerves (Gray[7]), and a superior cardiac nerve,[11] arising from the superior cervical ganglion (Hovelacque[12]). The plexus of the vertebral artery is formed principally from branches arising from the intermediate and the stellate ganglion.

The importance of the middle cervical ganglion in the sympathetic innervation of the upper extremity has already been pointed out by Foerster.[13] He suggested that the middle cervical ganglion may be a source of postganglionic neurons to the upper extremity and that such fibers would remain intact after stellectomy.

For these reasons, blocking of the anatomic and physiologic group consisting of the middle cervical, the intermediate and the stellate ganglions is essential if one is to obtain a maximum and complete interruption of the vasomotor pathways and the afferent pathways which arise from or cross these ganglions and are distributed in the fields over which the operation is to be done.

Study of the problem of stellate ganglion block resulted in my putting into practice a technical method of blocking the middle cervical and stellate ganglions by an anterior approach. This method has the following advantages: 1. It is devoid of the risk of vascular and pleuropulmonary accidents. 2. It has a deep point of osseous reference, easy to identify by palpation of the transverse process of the sixth cervical

7. Gray, H.: Anatomy of the Human Body, edited by W. H. Lewis, ed. 23, Philadelphia, Lea & Febiger, 1936.

8. Cunningham, D. J.: Textbook of Anatomy, edited by J. C. Brash and E. B. Jamieson, ed. 7, New York, Oxford University Press, 1937.

9. Huber, G. C.: Piersols' Human Anatomy, ed. 9, Philadelphia, J. B. Lippincott Company, 1930.

10. Morris, H.: Morris' Human Anatomy, edited by J. P. Schaeffer, ed. 10, Philadelphia, The Blakiston Company, 1942.

11. Ranson, S. W.: The Anatomy of the Nervous System, Philadelphia, W. B. Saunders Company, 1943.

12. Hovelacque, A.: Anatomie des nerfs craniens et rachidiens et du systeme grand sympathique chez l'homme, Paris, Gaston Doin & Cie, 1927.

13. Foerster, O.: Ueber Störung der Thermoregulation bei Erkrankungen des Gehirns und Rückenmarks und bei Eingriffen am Zentralnervensystem, Jahrb. f. Psychiat. u. Neurol. **52**:1, 1935.

vertebra. 3. The maximum effect is produced by blocking not only the stellate ganglion but the intermediate and the middle cervical ganglion.

PROPOSED TECHNICS FOR BLOCKING THE STELLATE GANGLION

The anterior approach was described, in 1934, by Leriche and Fontaine.[3] The patient having been placed in dorsal decubitus, with the head raised a little with a pillow and turned to the opposite side, the needle is inserted at the level of the superior border of the clavicle, in the direction of the transverse process of the seventh cervical vertebra. As soon as the tip of the needle is in contact with the bone, a double change of direction is made. By elevation of the hub of the needle, its tip is lowered by an amount corresponding to the height of a vertebra; and, with a rotational movement of 30 degrees, it is carried to the extremity of the horizontal plane. These maneuvers should bring the tip of the needle close to the stellate ganglion.

Practice of this technic showed that it was difficult to obtain anesthesia of the stellate ganglion without the frequent appearance of vascular, neurologic or pleuropulmonary complications. Moreover, the patients complained many times of a deep painful sensation at the time of insertion of the needle, which left an unpleasant impression and caused them to submit unwillingly to repeated blocks of the stellate ganglion.

Lambret, Razemon and Decoulx[2] admitted that the anterior approach of Leriche and Fontaine[3] is an easy and effective method but stated that it is inconvenient in that its points of reference do not offer the desired precision. This disadvantage was also indicated in the investigations of Malherbe (cited by Lambret and associates[2]), who proposed to infiltrate the stellate ganglion under roentgenoscopic control. Leriche observed also in his patients, especially persons with a short neck, asthma and emphysema, accidents such as perforation of the pleural cupula, the vertebral artery or the brachial plexus. Later Leriche[14] expressed the opinion that the topographic relations of the stellate ganglion in the patient were different from those in the cadaver. Observations made in the course of stellectomy and roentgenographic study revealed that the stellate ganglion, in spite of its contact with the first rib, and by virtue of the forward obliquity of this rib, was purely a cervical organ, even though theoretically it was a thoracic structure. Roentgenographic study of the needle inserted 2 fingerbreadths above the clavicle demonstrated that the tip of the needle touched the transverse process of the seventh cervical vertebra or the neck of the first rib with regularity. Leriche described the technic which he follows. Two fingerbreadths above the clavicle he inserts a needle 8 to 9 cm. long in the direction of the osseous plane, and with a slight downward slant. When the needle is in the right position, it is usually sufficient to inject 10 cc. of 1 per cent solution of procaine hydrochloride, or 20 cc. if one is not certain of the position of the needle.

Goinard (cited by Lambret and co-workers[2]) practiced an external route of approach, the principal point of reference being the curvature of the first rib, in the supraclavicular fossa. The needle is inserted laterally, immediately above the first rib, into the anterior border of the trapezius muscle and is directed toward the rib with an inclination of 45 degrees. As soon as it reaches the osseous plane, it is advanced in contact with the rib, until it impinges on the body of the vertebra, where the stellate ganglion is located. With the technic of Goinard, identification of the first rib is difficult when excessive accumulation of fat is present in the supraclavicular fossa. Moreover, insertion of the needle in the direction of the intervertebral foramen involves the risk of the anesthetic penetrating into the vertebral canal.

Arnulf[4] used a superoexternal approach to obtain, with the same insertion, anesthesia of the stellate ganglion and of the first dorsal ganglion. The needle is inserted 5 cm. above the junction of the inner and the middle third of the clavicle, at the level of the posterior border of the sternocleidomastoid muscle. After the fingers have been placed on the supraclavicular fossa, against the prevertebral osseous plane, the needle is inserted obliquely backward and downward, toward the transverse process of the seventh cervical vertebra. The needle is then inclined vertically, and its tip descends in contact with the body of the vertebra. It is made to penetrate from 8 to 9 cm. In this manner it is possible, according to Arnulf, to obtain anesthesia of the stellate and of the first thoracic ganglion. In my first trial with this technic, the needle penetrated the vertebral artery. Moreover, it is relatively easy for the needle, in its progress downward, to cross the pleural cupula and to penetrate the pleural cavity, or even the lung. Also, the deep points of reference are not

14. Leriche, R.: La chirurgie de la douleur, ed. 2, Paris, Masson & Cie, 1940.

always easy to palpate at the level of the seventh cervical verterbra. For these reasons I abandoned this technic.

In 1939 Ochsner and DeBakey [15] described a method for stellate ganglion block by the anterior approach which is a modification of the technic of Leriche and Fontaine.[3] A needle 80 mm. in length is inserted at a point 1 cm. medial to the midpoint of the clavicle and parallel with its superior border; it is directed horizontally, posteriorly and medially at an angle of 45 degrees with the median sagittal plane. When the point of the needle reaches a depth of 6 to 7 cm., it impinges on the anterolateral surface of the body of the seventh cervical vertebra or on the junction of the seventh cervical and the first thoracic vertebra, where the stellate ganglion lies. Ten cubic centimeters of 1 per cent solution of procaine hydrochloride is injected.

Recently Volpitto and Risteen [16] proposed a new anterolateral approach to the stellate ganglion. Their technic is similar to that of Leriche and Fontaine[3] and Ochsner and DeBakey.[15] The seventh cervical transverse process is identified, and a cutaneous wheal is raised 1 cm. above the midpoint of the clavicle. A needle 80 mm. in length is advanced at a 45 degree angle with the sagittal plane of the body downward and medially toward the seventh cervical transverse process. When contact with bone is made, the needle is withdrawn slightly and reinserted downward and inward to insure that the point of the needle is on the first rib. The needle is advanced 1 to 2 cm. until it impinges on bone, and 5 cc. of 1 per cent solution of procaine hydrochloride is slowly injected at this point. The authors stated that they have used this technic successfully in approximately five hundred injections. Owing to the movements which the tip of the needle makes close to the transverse process of the seventh cervical vertebra and to the neck of the first rib, there is a risk that the needle will wound the vertebral artery or the pleura. This approach possesses the advantages and the inconveniences of the technic of Leriche and Fontaine.[3]

In November 1944 Murphey [17] described a new anterior approach for stellate ganglion block. The patient is placed in a supine position on a firm bed, and the cricoid cartilage and the scalenus anticus muscle are identified by palpation. A spinal puncture needle is inserted at the lateral edge of the scalenus anticus muscle, at the level of and with the point directed toward the cricoid cartilage. If the needle were inserted with the point directed posteriorly so that the shaft made an angle of from 5 to 15 degrees with the horizontal plane, the needle would pass behind the great vessels and come into contact with the body of the seventh cervical vertebra at a depth of 3, 5 or 6 cm. Ten cubic centimeters of a 2 per cent solution of procaine hydrochloride is then injected. With this approach Murphey observed few complications; there were transitory pain when the deep fascia was pierced and occasional hypesthesia and paresis of the spinal nerves of the corresponding upper extremity, and in 1 case the needle entered the subarachnoid space.

Besides the anterior, the external and the superoexternal approach to the stellate ganglion, there have been reported technics in which this ganglion was reached through the posterior route. Mandl,[5] in 1925, produced for the first time paravertebral anesthesia of the stellate ganglion through the posterior approach. Later there appeared the technics of White and associates [18] and Wertheimer and Trillat.[1]

White [6e] places the patient on his side and injects procaine intradermally 4 cm. lateral to the seventh cervical and the upper three thoracic spinous processes. Needles 10 cm. long are then inserted at these points and pushed inward in a direction perpendicular to the skin until the transverse process or the rib is touched, at an average depth of from 2 to 5 cm. It is important (White) to visualize the depth of the ribs in order not to penetrate the pleura and puncture the surface of the lung. Then the tip of the needle is manipulated caudalward until it touches the lower border of the transverse process; the tip of the needle is then 3 cm. from the skin. Each needle is then inclined 20 degrees with the median sagittal plane; when it is thrust inward at this angle, a second contact is made with bone at a further depth of 3 cm. Two cubic centimeters of 2 per cent solution of procaine hydrochloride should be injected through each needle; when signs of paralysis of the sympathetic nerves appear, lasting paralysis is obtained with injection of 5 cc. of 95 per cent alcohol through each needle.

With the technic of Wertheimer and Trillat [1] the point of reference is the first rib, the needle being inserted across the internal part of the first intercostal space. Five or 6 cm. lateral to the

15. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocaine Block of Sympathetics: Technique of Injection, Surgery **4**:491, 1939.

16. Volpitto, P. P., and Risteen, W. A.: Stellate Ganglion Block: A Definite Anterolateral Approach, Anesthesiology **5**:491, 1944.

17. Murphey, D. R.: Stellate Ganglion Block: A New Anterior Approach, Ann. Surg. **120**:759, 1944.

18. White and White.[6a] White, Garrey and Atkins.[6b] White (footnotes 6*c*, *d* and *e*).

spinous process of the first dorsal vertebra, the needle is directed horizontally and inwardly at a certain angle. After having crossed the soft parts, it reaches the transverse process of the first dorsal vertebra. The needle is withdrawn a little and is then oriented in a manner so as to pass above the process, and is pushed forward 2 or 3 cm. New resistance is then encountered, which may be the vertebral body or the head of the first rib. After the needle is withdrawn a little, injection of the anesthetic proceeds.

There exist variations of these technics, such as the methods which were proposed by Paraf and Dreyfus, Le Foyer, and Demarez (cited by Lambret and associates [2]). The first two authors inserted the needle at the level of the seventh cervical spinal process, 4 cm. from the median line. The needle, after having passed around the superior border of the first rib, is advanced about 1 cm., and injection of the anesthetic is begun immediately. With the technic of Demarez the needle is also inserted 4 cm. from the sagittal plane, but at the level of the spinous process of the first dorsal vertebra. Any of these posterior approaches offers less risk and is generally better tolerated than are the anterior approaches.

Lambret, Razemon and Decoulx [2] pointed out various reasons that the posterior approaches are safer: precise osseous points of reference; no necessity of changes in direction of the needle; maneuvers with the needle in the wall of the torso, and periganglionic infiltration of the loose connective tissue of the precostal space. The anterior approach is definitely indicated for patients who cannot be moved because of their condition.

Until 1939 my preference vacillated between the anterior approach of Leriche and Fontaine and the posterior approach (Mandl [5]; White and White [6a]), which I used when the morphology of the base of the neck contraindicated employment of the anterior route. It happened, however, that with the anterior approach, not only did vascular, pleural and neural accidents occur from time to time, but infiltration anesthesia was not followed by block of all communicating branches of the brachial plexus, particularly those arising from the middle cervical ganglion.

Also, block of the cervicothoracic sympathetic pathways with any of the technics in which the posterior approach is used (Mandl,[5] White and associates [18] and Wertheimer and Trillat [1]) is limited to the stellate ganglion and to the superior (second, third and fourth) thoracic sympathetic ganglions. The intermediate ganglion, located above and close to the vertebral artery; the middle cervical ganglion, located on a level with the sixth cervical vertebra, as well as the communicating branches of these two ganglions, and the middle cardiac nerve are not blocked when

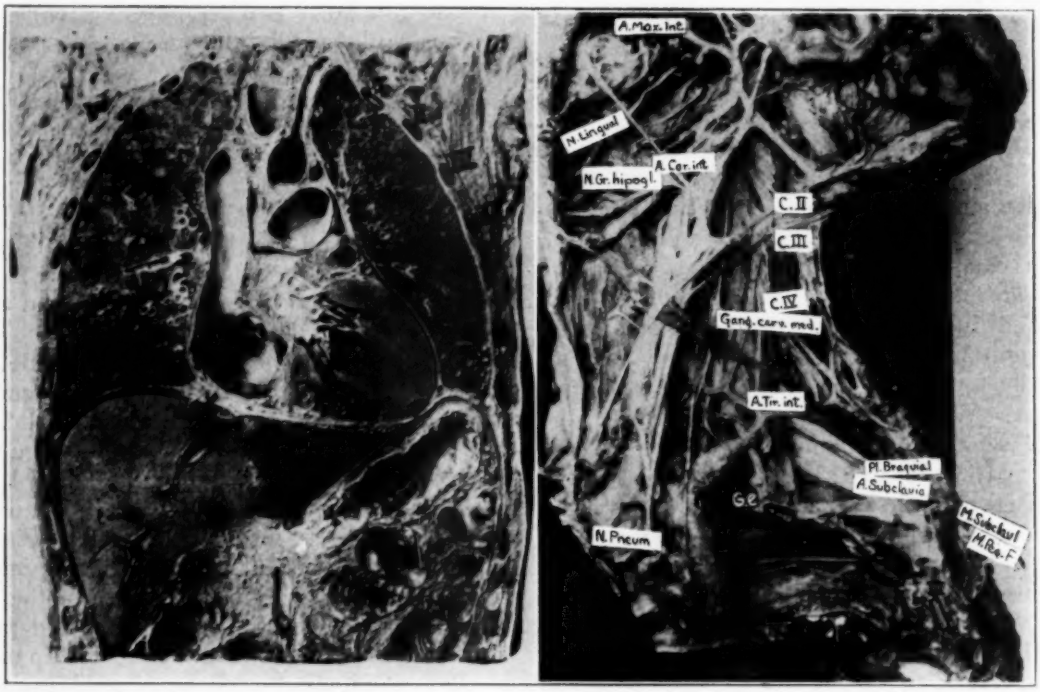

Fig. 2.—Relations of the pulmonary vertex and of the pleura to the first rib (*I*). The stellate ganglion (*Ge*) occupies a deep suprapleural and retropleural location, behind the vertebral and subclavian arteries.

the anesthetic is injected dorsally at the level of the first intercostal space or below.

After reviewing the various methods for block of the sympathetic ganglions, I studied carefully the topography and the relations of the middle cervical, intermediate and stellate ganglions to the skeleton, to the vessels and to the pleural cupula and tried to devise a technic by which anesthesia of these ganglions could be obtained with minimum risk to the patient and with maximum probability of success.

MORPHOLOGY AND RELATIONS OF THE MIDDLE CERVICAL AND STELLATE GANGLIONS

The stellate ganglion, which results from fusion of the inferior cervical and the first thoracic sympathetic ganglion, constitutes a physiologic entity characterized by its relations to the cervicodorsal roots through the communicating branches. This ganglion appears in some

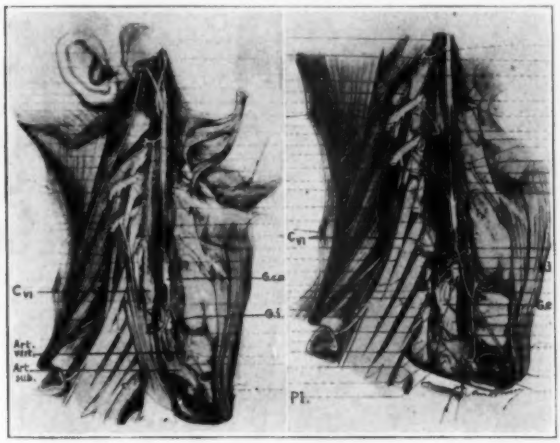

Fig. 3.—Relations of the intermediate (*G.i.*) and the stellate ganglion (*G.e.*) to the vertebral artery, to the pleural cupula (*P.I.*) and to the transverse process of the sixth cervical vertebra. (*C VI*) (from Hovelacque [12]).

cases to be morphologically divided into two masses, the superoexternal (intermediate ganglion) and the posteroinferior (stellate ganglion). In a large number of cases it is oval and is elongated in a vertical direction, measuring from 1 to 2 cm. in length and 1 cm. in width. Located deep in the superior retropleural fossa (fig. 2), in relation to the vertebral artery and to the first rib, its situation is partly thoracic and partly cervical.

The stellate ganglion is located (fig. 3) in a concavity, which, according to Hovelacque, is limited inferiorly by the posterior aspect of the pleural cupula, medially by the portion of the vertebral column covered with the longus colli muscle of the neck, laterally by the scalenus muscle, posteriorly by the anterior surface of the transverse process of the seventh cervical vertebra and by the anterior surface of the neck of the first rib and anteriorly by the vertebral artery. The axis of the stellate ganglion is directed obliquely downward and inward, its posterior surface resting above on the transverse process of the seventh cervical vertebra and below on the neck of the first rib. In this position, the stellate ganglion is wrapped in a soft cellular-adipose tissue, which is easily separated when the stellate ganglion is isolated for the purpose of stellectomy.

The relations of the stellate ganglion to the vessels and the nerves must be understood.

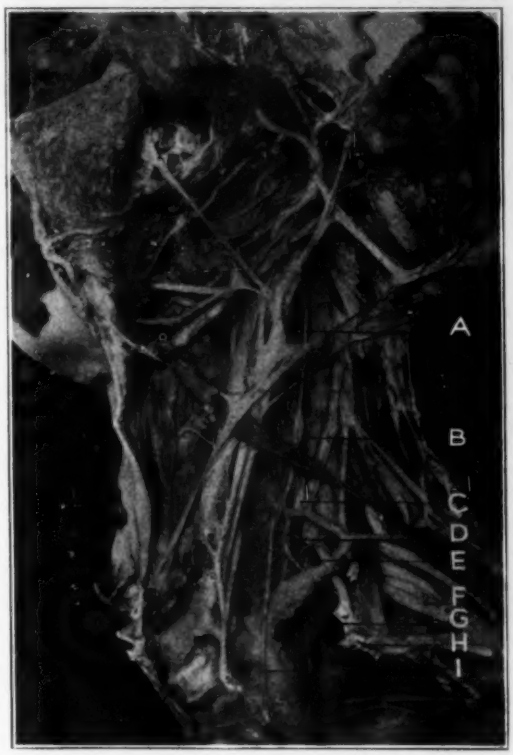

Fig. 4.—Dissection of the cervicothoracic sympathetic system, showing its intimate relations to the vertebral and subclavian arteries. *A*, cervical sympathetic trunk; *B*, middle cervical ganglion; *C*, sixth transverse process; *D*, intermediate sympathetic ganglion; *E*, vertebral artery; *F*, brachial plexus; *G*, stellate ganglion; *H*, first rib; *I*, middle cervical cardiac nerve.

Posteriorly it is in relation with the anterior branch of the eighth cervical nerve, and inferiorly, with the anterior branch of the first dorsal nerve. Its external border is crossed laterally by the intercostocervical arterial trunk, with which it sometimes is in contact. Anteriorly the stellate ganglion is related to the first segment of the vertebral artery (fig. 4). This relation varies according to whether the stellate

ganglion is composed of one mass only or of two masses, one being the intermediate ganglion. When the second ganglion is present, it is located above and medial to the principal mass and alongside and medial to the artery, both ganglions being united by nerve cords which surround the vertebral atery (fig. 5).

The middle cervical ganglion is located in front of the transverse process of the sixth cervical vertebra (fig. 3). From this ganglion arise the communicating branches for the fifth and sixth

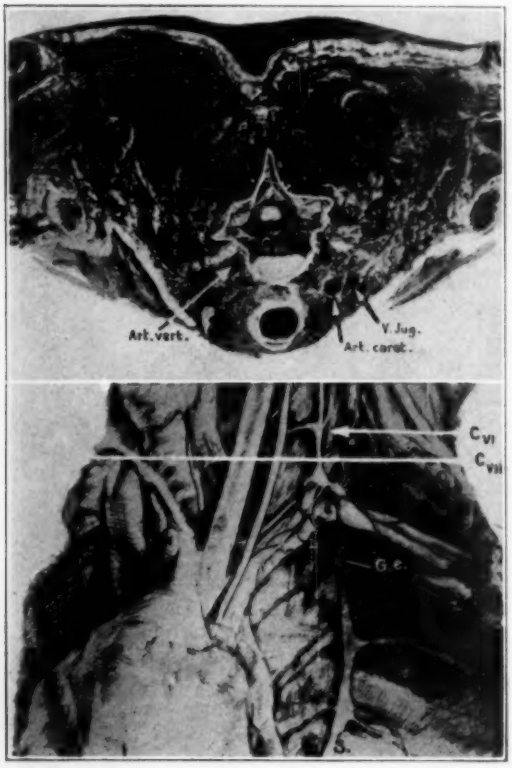

Fig. 5.—Section of the base of the neck made at the level of the seventh crevical vertebra (*C VII*). Notice the relations of the intermediate ganglion with the vertebral artery.

trunks of the brachial plexus and the middle cardiac nerve, the most developed of the three cardiac sympathetic nerves.

Besides the topographic relations of the stellate and middle cervical ganglions, it is also important to know the arrangement of the aponeurosis at the base of the neck, in order to understand the path of diffusion of the anesthetic solution injected, from the level of the transverse process of the sixth cervical vertebra to the position of the middle cervical and the stellate ganglion.

According to Hovelacque,[12] there exist a prevertebral aponeurosis, which covers the prevertebral muscles, and a deep aponeurosis, which envelops the viscera and the vessels before it joins the prevertebral aponeurosis. This disposition of the fascia exists only up to the level of the inferior thyroid artery; below that level the aponeurotic relations are changed, and it is difficult to speak of any closure thereafter. The cellular tissue is loose in front of the prevertebral aponeurosis in the whole inferior region of the neck (fig. 6). This anatomic disposition explains the reason that the anesthetic solution injected in front of the prevertebral aponeurosis, at the level of the sixth cervical transverse process, blocks the middle cervical ganglion and then descends into the prevertebral soft cellular tissue, to reach the stellate ganglion; through further diffusion in the soft cellular tissue surrounding this ganglion, the anesthetic causes block of the ganglion by periganglionic infiltration.

Fig. 6.—The space with soft cellular tissue located in the base of the neck (*5*), between the prevertebral aponeurosis and the posterior surface of the sheath which encloses the common carotid artery (*4*), the internal jugular vein (*2*) and the vagus nerve (*1*). In a posterior plane is the brachial plexus (*3*).

PRINCIPLES OF THE TECHNIC OF BLOCKING THE MIDDLE CERVICAL AND STELLATE GANGLIONS BY DESCENDING INFILTRATION ANESTHESIA

A study of the morphology, topography and relations of the stellate ganglion to the vessels and to the pleural cupula and experience acquired

with practice of the methods of infiltration previously explained led me to the conclusion that it was difficult to obtain anesthesia of the stellate ganglion, through the direct approach to this ganglion, without frequently causing a vascular or a pleural accident. Such a conclusion prompted the effort to block the stellate ganglion indirectly, by guiding the needle toward a fixed site easy of identification; it was believed that after the anesthetic solution was injected, it would diffuse downward from this site to anesthetize the middle cervical, intermediate and stellate ganglions.

Such a result was obtained by inserting the needle at the level of the base of the transverse process of the sixth cervical vertebra (fig. 7). In this manner the middle cervical ganglion is blocked and perforation of the vertebral artery is avoided. The anesthetic solution, being injected at the apex of the fossa of the stellate ganglion, descends by gravity and infiltrates the soft cellular tissue of the fossa. The stellate and intermediate ganglions and the respective communicating branches are saturated with the anesthetic solution; thus is obtained, simply and without accident, anesthetic block of the middle cervical, intermediate and stellate ganglions (fig. 8). As the communicating branches of the fifth and sixth cervical nerves cross and enter into close relation with the prevertebral muscle mass, this muscle mass is also anesthetized by infiltrating it with 5 cc. of anesthetic solution, which is injected anterior to the transverse process of the sixth cervical vertebra. This solution, injected into the muscular plane behind the prevertebral aponeurosis, also anesthetizes the sympathetic chain, which at this point lies anterior to the prevertebral aponeurosis. In front of this aponeurosis 15 cc. of the anesthetic solution is injected. The middle cervical ganglion is anesthetized, and the anesthetic solution diffuses in the soft cellular tissue of the fossa of the stellate ganglion and anesthetizes the ganglionic mass, together with the communicating branches to the seventh and eighth cervical nerves and the first dorsal nerve and the deep communicating branches which constitute the vertebral nerve.

In order to promote diffusion of the anesthetic solution, the injection is made with the patient seated or with the head and neck in an elevated position; this position brings the force of gravity into operation.

The point of osseous reference chosen is the base of the transverse process of the sixth cervical vertebra, and not the clavicle, since roentgenographic studies led to the conclusion that the position of the middle cervical and stellate ganglions in relation to the transverse process of the sixth cervical vertebra is less variable than its position in relation to the cavicle.

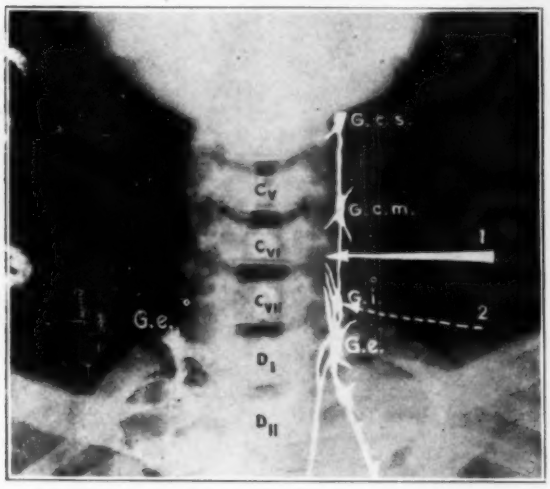

Fig. 7.—Relations of the cervical sympathetic ganglions (middle cervical ganglion, *G.c.m.*; intermediate ganglion, *G.i.* and stellate ganglion, *G.e.*) to the skeleton. (*1*) approach to the anterior surface of the sixth transverse process; (*2*) approach to the anterior surface of the seventh transverse process.

Fig. 8.—Descending infiltration anesthesia, made at the level of the sixth cervical transverse process, produces block of the middle cervical, intermediate and stellate ganglions. (*1*) middle cervical ganglion; (*2*) intermediate ganglion; (*3*) stellate ganglion; (*4*) second thoracic sympathetic ganglion.

TECHNIC OF BLOCKING THE MIDDLE CERVICAL AND STELLATE GANGLIONS BY DESCENDING INFILTRATION ANESTHESIA

The patient is seated facing forward, with his arms at his side. If the patient is not able to sit down, he is placed in dorsal decubitus, with the torso and head raised about 45 degrees; if he cannot look forward, his head is rotated to the side opposite the operator. The transverse process of the sixth cervical vertebra is palpated; this procedure presents difficulty only in patients with a short, fat neck.

After the skin is sterilized, a needle 6 to 8 cm. long, of small caliber, is inserted. The operator stands in front of the patient if the latter is sitting in an elevated position (table or bed), or rests on one knee if the patient is seated on a chair; he requests the patient not to contract the muscles of the neck or to move his head in the course of palpation or during insertion of the needle (fig. 9).

Fig. 9.—Technic of middle cervical and stellate ganglion block with descending infiltration anesthesia.

With the tip of the left index finger pointing in an anteroposterior direction, the anterior surface of the transverse process of the sixth cervical vertebra is palpated behind the posterior border of the sternocleidomastoid muscle. With this maneuver, one tries to displace the sternocleidomastoid muscle, the larynx and trachea and the neurovascular bundle of the neck as much as possible toward the midline and over the prevertebral plane. With this displacement, the skin is strongly depressed over the anterior surface of the transverse process of the sixth cervical vertebra, and the end of the index finger is fixed against the osseous plane, thus furnishing the deep point of reference against which it is necessary to direct the tip of the needle. The needle is inserted in the anteroposterior direction almost perpendicularly toward the anterior surface of the transverse process of the sixth cervical vertebra and directed toward the base of this process, where the sympathetic chain crosses it. If the needle is directed toward the tip of the transverse process, diffusion of the anesthetic solution will cause anesthesia of the brachial plexus.

In order to make certain that the needle is in a correct position, it is necessary to feel its point in contact with the bone. As soon as the correct position is obtained, pressure on the hub of the needle is continued, in order to maintain the tip in contact with the process, and with the left hand the depressed skin is slid along the needle, so that the latter will remain in contact with bone when the pressure is released. As soon as the left hand releases its hold on the sternocleidomastoid muscle and the neurovascular bundle, the needle, which had been inserted in an anteroposterior direction, is displaced by the recoil of these structures to the horizontal plane; as a result, it lies in a somewhat lateral, and at times a transverse, position.

After preliminary aspiration to exclude bleeding, 5 cc. of 1 per cent solution of procaine hydrochloride is injected against the anterior surface of the base of the transverse process; the anesthetic diffuses between the process and the prevertebral aponeurosis and descends to reach the external layer of the vertebral artery and the branches of the vertebral nerve. The tip of the needle is

then slowly withdrawn for about 2 or 3 mm., until it is felt to be out of the resistant prevertebral aponeurosis and to be free in the soft cellular tissue which lies in front of this aponeurosis. After a second aspiration to exclude bleeding, 15 to 20 cc. of 1 per cent procaine hydrochloride solution is injected at this point. The anesthetic blocks the middle cervical ganglion, and the solution, descending in front of the prevertebral aponeurosis, in which is located the cervical sympathetic chain, diffuses in the soft cellular tissue which surrounds the vertebral artery and the intermediate and the stellate ganglion. Normally, the middle cervical ganglion; the interganglionic trunk which unites the stellate ganglion and the middle cervical ganglion; the intermediate ganglion, when it is present; the stellate ganglion and all its communicating branches, including the vertebral nerve, are all blocked by the anesthetic solution, which diffuses downward in this plane under the force of gravity.

If during the fifteen minutes which follows injection of the anesthetic there do not appear signs of vasomotor and pain block of the sympathetic innervation of the upper extremity and thorax, however evident are the signs of cephalic sympathetic block, it is apparent that the anesthetic did not diffuse sufficiently (the needle was not placed in the right position, or pathologic conditions of the tissues existed) to block completely the stellate ganglion. In this case, if the inferior cervical sympathetic block is made to interrupt the sympathetic innervation of the upper extremity or of the thoracic organs, the first injection of the anesthetic, made at the level of the sixth transverse process, must be followed by a second insertion, with the needle directed toward the base of the transverse process of the seventh cervical process. The transverse process of the sixth cervical vertebra is identified, and the structures are retracted, as in the technic previously described. An insertion is made about 1.5 to 2 cm. below the transverse process of the sixth cervical vertebra, and the needle is directed toward the base of the transverse process of the seventh cervical vertebra. When the puncture is made at this point, the needle must penetrate deeper than when it is inserted at the level of the sixth cervical vertebra. All the other details of the technic are similar to those which have already been described for insertion at the level of the sixth cervical transverse process. Five cubic centimeters of 1 per cent procaine hydrochloride solution is injected against the osseous plane, and 10 cc. more of the same drug is injected 2 or 3 mm. in front of this plane, into the soft connective tissue. In this case the tip of the needle normally is close to the intermediate ganglion and the vertebral artery. For this reason the greatest care must be taken not to inject the anesthetic into the vertebral artery. In this way it is possible to obtain safe block of the middle cervical, the intermediate and the stellate ganglion.

Several drugs with a more prolonged action have been proposed as substitutes for procaine in blocking sympathetic ganglions. Novest-Oil [19] was used by Brenner [20] for prolonged analgesia in a group of cases of rectal disorders, and it was also employed by Belinkoff [21] for intercostal block in operations on the upper part of the abdomen. Recently Lee [22] employed monobromosalicyl alcohol for the purpose of obtaining prolonged anesthesia of the stellate and lumbar sympathetic ganglions. The value of this drug, according to Lee, is in its reducing the number of injections required in cases in which repeated sympathetic block is indicated.

In cases in which blocking of the stellate ganglion must be done at short intervals I have employed a solution of 1 per cent procaine hydrochloride. Such blocks were always well tolerated by the patient, were followed by satisfactory results and did not produce neuritis. In cases in which stellectomy was done, after repeated blocks, no difficulty either in the approach to or in the isolation of the stellate ganglion was encountered. The only abnormality noted was that the operative wound bled more than usual, owing to vasodilatation.

CLINICAL SIGNS INDICATIVE OF SUCCESS OF BLOCK OF THE MIDDLE CERVICAL AND STELLATE GANGLIONS

A few minutes after injection of the anesthetic solution, the patient begins to show signs of the Bernard-Horner syndrome (fig. 9). There are miosis of the pupil, ptosis of the upper lid and slight elevation of the lower lid, with narrowing of the palpebral fissure, and enophthalmos. The conjunctiva becomes congested, owing to vasodilatation of its vessels. These signs become progressively accentuated for fifteen or twenty

19. Novest-Oil is a solution of monoisobutylaminoethylparaaminobenzoate hydrochloride base, benzyl alcohol and ethyl aminobenzoate in expressed oil of almond.

20. Brenner, J. M.: Novest-Oil: A New Prolonged Oil Analgesic, J. Nat. Proct. A. **14**:244, 1942.

21. Belinkoff, S.: Intercostal Block with Long-Acting Anesthetic in Upper Abdominal Operations, Anesthesiology **5**:500, 1944.

22. Lee, C. F.: Am. J. M. Sc., 1945, to be published. Lee, C. F.; Macht, D. I., and Pierpont, R. Z.: A Preliminary Report on a Method for Lengthening the Effect of a Sympathetic Nerve Block, Bull. Johns Hopkins Hosp. **74**: 119, 1944.

minutes, when they present their maximum intensity. About one hour later they begin to diminish and to disappear.

The face and the ear on the side of block of the stellate ganglion often become red, and the patient feels a burning sensation. Anhidrosis is observed on the same side of the head and the corresponding upper extremity. In the upper extremity, especially the hand, the patient feels a burning sensation. The hand and the forearm become warm, signs of vasodilatation being seen at the level of the fingers.

The oscillometric index for the arm and forearm is increased after block of the middle cervical and stellate ganglions.

ACCIDENTS WHICH MAY OCCUR IN THE COURSE OF BLOCKING THE MIDDLE CERVICAL AND STELLATE GANGLIONS

It was the frequency of pleuropulmonary and vascular accidents, such as perforation of the subclavian or vertebral arteries, which led me to abandon the technic of stellate ganglion block by direct injection into this ganglion.

With the technic which I have employed for five years, in hundreds of cases, no pleuropulmonary accident has been observed. Only occasionally has the inferior thyroid or the vertebral artery been punctured; this accident was especially likely to occur when the tip of the needle was directed toward the base of the transverse process of the seventh cervical vertebra. Besides always employing a fine needle, I make it a rule to aspirate before injecting the anesthetic solution, in order to avoid intra-arterial injection.

I have never entered the intervertebral foramen, since I am careful to insert the needle in an anteroposterior direction and to keep the tip in contact with the anterior surface of the transverse process during the external rotation which it undergoes when the sternocleidomastoid muscle returns to its resting position.

It is possible for the needle to perforate the trunk of one of the cervical nerves if, instead of passing in the direction of the transverse processes of the sixth and seventh cervical vertebrae, it penetrates the space between the transverse processes of these vertebrae. In order to avoid this accident, the tip of the needle is directed toward the base of the transverse process.

I have never observed any complications other than a slight vertiginous condition in a few patients, which did not necessitate special care and which disappeared completely within one hour after the block.

THERAPEUTIC INDICATIONS FOR BLOCK OF THE MIDDLE CERVICAL AND STELLATE GANGLIONS WITH AN ANESTHETIC

Since the investigations initiated in 1925 by Leriche and Fontaine [3] on the clinical indications for and the technic of block of the stellate ganglion, the field in which this therapeutic measure has shown its valuable results has expanded considerably.

Therapeutic indications for block of the middle cervical and the stellate ganglion are deduced from knowledge [23] of the influence which physiologic interruption of these glanglions exerts on the organs which they innervate. Blocking of these ganglions produces a vasomotor effect which is evident in the corresponding half of the head, face and neck; it extends to the heart and to the respiratory apparatus and from the larynx to the bronchial extremities (Leriche [14]), and it is intense in the arm on the same side. This vasomotor effect is of much longer duration than that produced by simple anesthesia. The vasomotor change consequent on blocking of the middle cervical and stellate ganglions is of the nature of vasodilatation, with increase in the local temperature, the oscillometric index and the peripheral circulation.[24] These effects constitute important indications for its use in the relief of vasoconstriction in any zone innervated by these ganglions or in the activation of the circulation when it is locally decreased.[25]

Thus, in cases of cerebral vasospasm, the indication for block of the middle cervical and stellate ganglions is based on the physiologic interruption of cerebral vasomotor pathways. Investigations of several authors (Orr and Sturrock,[26]

23. Braeucker, W.: Der Brustteil des vegetativen Nervensystems und seine klinisch- chirurgische Bedeutung, Beitr. z. Klin. d. Tuberk. **66**:1, 1927. Gask, G. E.: The Surgery of the Sympathetic Nervous System, Brit. J. Surg. **21**:113, 1933. Kuntz, A.: Autonomic Nervous System, Philadelphia, Lea & Febiger, 1934.

24. de Sousa Pereira, A.: L'infiltration novocainique du ganglion étoilé: Bases expérimentales et applications cliniques, Arch. d. mal. du cœur, 1941, p. 1.

25. Bird, C. E.: Sympathectomy as Preliminary to Obliteration of Popliteal Aneurism, Surg., Gynec. & Obst. **60**:926, 1935. Gage, M.: Mycotic Aneurism of the Common Iliac Artery: Sympathetic Ganglion Block as an Aid in the Development of the Collateral Circulation in Arterial Aneurism of the Peripheral Arteries, Am. J. Surg. **24**:667, 1934. Lehman, E. P.; Rawles, B. W., and Murphey, D. R.: Sympathectomy in Acute Arterial Occlusion: An Experimental Study, South. M. J. **26**: 246, 1933. Theis, F. V.: Effect of Sympathetic Neurectomy on the Collateral Arterial Circulation of the Extremities: Experimental Study, Surg., Gynec. & Obst. **57**:737, 1933.

26. Orr, D., and Sturrock, A. C.: Toxi-Infective Lesions in the Central Nervous System: The Influence of Disturbance of the Sympathetic Mechanism on Their Localization, Lancet **2**:267, 1922.

Forbes and associates,[27] Talbot and co-workers,[28] Cobb,[29] Chorobski and Penfield[30]) have shown that innervation of the cerebral vessels is similar to that of the arterial systems in other regions and organs. Interruption, by block of the middle cervical and stellate ganglions, of the sympathetic innervation of cerebral vessels produces vasodilation of the cerebral vessels on the same side of the brain. Volpitto and Risteen,[31] by direct inspection of the cortex of 2 patients immediately after block of the stellate ganglion, noted an increase in the caliber of the pial vessels. These authors observed that patients with a condition diagnosed as cerebral thrombosis showed improvement immediately or several hours after block of the stellate ganglion with procaine. This improvement varied from partial to complete recovery. Also, a patient with frequent attacks of cerebral vasospasm showed great improvement immediately after block of the stellate ganglion. In cases of thrombosis of the posterior inferior cerebellar artery, the reflex spasm is abolished and dilation of collaterals is produced by block of the stellate ganglion with procaine (Hickcox, Tovell, Raskind and Scoville[32]).

In cases of circulatory disturbances[33] of the upper extremity in which there is ischemia[34] and in cases of arterial embolism,[35] thrombophlebitis,[36] atonic ulceration, post-traumatic edema[37] and post-traumatic osteoporosis, good results have been obtained with repeated blocks of the middle cervical and stellate ganglions with procaine. In the reflex arteriospasm which accompanies the embolic phenomenon, the pain may be relieved and the collateral circulation increased by interruption of the vasoconstrictor fibers through blocking the middle cervical and stellate ganglions with procaine. According to Hickcox and co-workers,[32] the arteriospasm in Raynaud's disease or an acute arteriospasm, traumatic in origin or associated with the embolic phenomenon may be relieved by stellate ganglion block.

Asthmatic crises have been relieved by means of stellate ganglion block, possibly through vasomotor control, which produces changes in the bronchial and tracheal mucosa, and through action on the bronchial muscles (Leriche). A favorable therapeutic result was obtained by Fontaine in cases of acute edema of the lung. The effect of this procedure has also been studied in cases of experimentally induced pulmonary embolism.

Concerning the influence of stellate ganglion block on coronary[38] and heart disease,[39] Leriche[14] stated that in cases of angina pectoris and tachycardia the painful phenomena disappear and the rhythm of the heart is regularized. In the treatment of cardiac pain in angina pectoris, White and associates[6] stated they preferred alcoholization of the stellate ganglion and of the second, third and fourth thoracic ganglions to repeated blocks with procaine. With the paravertebral block of Mandl[5] or with the alcoholization of the stellate and upper thoracic ganglions (Swetlow,[40] White and co-workers,[41]

27. Forbes, H. S., and Wolff, H. G.: The Cerebral Circulation: III. The Vasomotor Control of the Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928. Forbes, H. S., and Cobb, S.: Vasomotor Control of Cerebral Vessels, Brain **61**:221, 1938.

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29. Cobb, S.: The Cerebral Circulation: IX. The Relationship of the Cervical Sympathetic Nerves to Cerebral Blood Supply, Am. J. M. Sc. **178**:528, 1929.

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31. Volpitto, P. P., and Risteen, W. A.: The Use of Stellate Ganglion Block in Cerebral Vascular Occlusion, Anesthesiology **4**:403, 1943.

32. Hickcox, C. B.; Tovell, R. M.; Raskind, R., and Scoville, W. B.: The Stellate Ganglion: Its Significance in Practice, Anesthesiology **4**:150, 1943.

33. Burns, Shock, Wound Healing and Vascular Injuries, Military Surgical Manuals, National Research Council, Philadelphia, W. B. Saunders Company, 1943, vol. 5.

34. Leriche, R.: Les maladies des ligaturés; moyens de les prévenir et de les traiter, Presse méd. **48**:41, 1940.

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37. de Sousa Pereira, A., and Fontaine, R.: Edema duro post-traumatico curado por infiltracoes locais e do ganglio estrelado, Portugal méd., 1936.

38. Flothow, P. G.: Diagnostic and Therapeutic Injections of Sympathetic Nerves, Am. J. Surg. **14**: 591, 1931. Marvin, H. M.: Surgical Treatment of Angina Pectoris, Bull. New York Acad. Med. **11**:453, 1935. Miller, H. R.: Angina Pectoris: Nerve Pathways, Physiology, Symptomatology and Treatment, Baltimore, Williams & Wilkins Company, 1939. Ochsner, A., and DeBakey, M.: The Surgical Treatment of Coronary Disease, Surgery **2**:428, 1937.

39. Mackenzie, J.: Diseases of the Heart, ed. 4, New York, Oxford University Press, 1925.

40. Swetlow, G. I.: Paravertebral Alcohol Block in Cardiac Pain, Am. Heart J. **1**:393, 1926; Angina Pectoris: Paravertebral Alcohol Block for Relief of Pain, Am. J. Surg. **9**:88, 1930.

(Footnotes continued on next page)

Lundy,[42] Seldon,[43] Woodbridge,[44] Levy and Moore [45] and Peterson [46]) some favorable results have been obtained in the treatment of the cardiac pain of angina pectoris. Brown-Séquard paralysis following a paravertebral injection of alcohol for angina pectoris was observed in 1 case (Molitch and Wilson [47]).

At present, I am using, in a systematic way, block of the middle cervical and stellate ganglions in all cases of angina pectoris for the purpose of establishing an indication for stellectomy. However, in the investigation of the pathways for painful sensations associated with angina pectoris, it must be remembered that blocking of the middle cervical and of the stellate ganglion is not sufficient. In cases of angina pectoris with coronary insufficiency I have observed the appearance of anginal crisis during blocking of the left middle cervical and stellate ganglions. In these cases immediate blocking of the left splanchnic nerves abolished the anginal crisis quickly. Since these observations, in all cases of angina pectoris in which repeated block of the middle cervical and stellate ganglions with procaine did not abolish or modify the anginal crisis, I have always blocked the splanchnic nerves, beginning with those on the left side. Within the limits of this experimental work, it was possible to find a few cases of angina pectoris in which block of the left middle cervical and stellate ganglions was not effective and a few cases in which block of the left splanchnic nerves abolished the crisis temporarily. Splanchnicectomy performed in these cases confirmed the indication furnished by the block, since the anginal crisis disappeared completely. These observations prove the existence of cases of angina pectoris in which stimuli arising in the solar plexus are transmitted along the splanchnic nerves, particularly on the left side, and reach the heart, through the cardiac branches [48] of the second, third and fourth thoracic sympathetic ganglions.[49] In these cases blocking of the middle cervical ganglion and of the stellate ganglion is insufficient to abolish the anginal crisis. Only associated blocking of the second, third and fourth thoracic ganglions, which White does, or blocking of the splanchnic nerves or splanchnicectomy, which I have done, abolishes the anginal crisis when stimuli which precipitate the crisis arise in the solar plexus.

In cases of facial paralysis of peripheral type, without anatomic lesions of the trunk of the facial nerve, repeated block produced favorable results. Also, in some cases post-traumatic paralysis of the radial and ulnar nerves [50] without anatomic lesions, even when it appeared several weeks after the accident, disappeared in a few weeks with repeated block of the middle cervical and stellate ganglions. The favorable results obtained in these cases must perhaps be interpreted as a consequence of improvement in the circulation of the trunk of the paralyzed nerve produced by block of the cervical sympathetic ganglions.

Block of the middle cervical and stellate ganglions has shown its usefulness as a therapeutic method in the relief of pain, as a means of analyzing the sympathetic conduction of pain and as a preoperative test for stellectomy in cases of thoracic pain and pain of the upper extremity and the head.[51]

In the syndrome of pain associated with trophic changes, known as causalgia (Mitchell [52]), the pain results in arterial spasm, which intensi-

41. Bland, E. F., and White, J. C.: Relief of Severe Angina Pectoris in Young People with Rheumatic Heart Disease, with Remarks on an Atypical Anginal Syndrome, New England J. Med. **215**:139, 1936; footnote 6.

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45. Levy, R. L., and Moore, R. L.: Paravertebral Injections of Alcohol for the Relief of Cardiac Pain: A Review of Experience to Date and a Report of Nine Cases, Arch. Int. Med. **48**:146 (July) 1931; Paravertebral Sympathetic Block with Alcohol for the Relief of Cardiac Pain: Report of Forty-Five Cases, J. A. M. A. **116**:2563 (June 7) 1941.

46. Peterson, M. C.: Paravertebral Alcohol Injection for Cardiac Pain, Anesth. & Analg. **17**:35, 1938.

47. Molitch, M., and Wilson, G.: Brown-Séquard Paralysis Following a Paravertebral Alcohol Injection for Angina Pectoris, J. A. M. A. **97**:247 (July 25) 1931.

48. Kuntz, A., and Morehouse, A.: Thoracic Sympathetic Cardiac Nerves in Man: Their Relation to Cervical Sympathetic Ganglionectomy, Arch. Surg. **20**: 607 (April) 1930.

49. de Sousa Pereira, A.: A existencia fora do ganglio estrelado de vias simpaticas de inervacao cardiaca, Reun. cient. Fac. med. do Pôrto, January-March 1944.

50. de Sousa Pereira, A.: A influência das infiltrações novocaínicas repetidas do gânglio estrelado num caso de paralisia do nervo cubital, Lisboa méd. **14**:1, 1937.

51. Davis, L., and Pollock, L. J.: The Role of the Sympathetic Nervous System in the Production of Pain in the Head, Arch. Neurol. & Psychiat. **27**:282 (Feb.) 1932.

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fies the painful sensation.[53] In the early stages of this disease, block of the middle cervical and stellate ganglions may contribute to the relief of pain. In movements of the shoulder joint during the period following arthritis, arthrotomy or arthroplasty, block of the middle cervical and stellate ganglions relieves the sympathetic pain arising in the capsule and ligaments of the joint.

I am trying to determine the value of blocking the middle cervical and stellate ganglions to relieve the sympathetic pain arising from an operative wound in the thoracic viscera and to inhibit the sympathetic vasomotor reflexes which arise in the wound and contribute to the shock of the operation. It is known at present that with surgical trauma the vasoconstriction which is associated with disturbances such as pain is probably one of many factors in the genesis of shock (Blalock[54]).

In cases of painful edema of the upper extremity,[55] observed immediately after amputation of the breast for cancer, with extirpation of the lymphatic nodes of the axilla, repeated blocks of the middle cervical and stellate ganglions cause the pain to disappear, with immediate vasomotor modification, rapid disappearance of the edema and prompt recovery of function of the extremity. In cases of pain associated with inoperable cancer of the mammary gland,[55] due to neoplastic lymphangitis, block of the middle cervical and stellate ganglions is followed by temporary disappearance of pain resulting from irritation of the sympathetic perivascular innervation. In these cases block of the middle cervical and stellate ganglions is especially important as a method of analysis of the mechanism of pain and as a preoperative test to define the indication for stellectomy.

SUMMARY

The vascular, neural and pleuropulmonary accidents observed in the course of stellate ganglion block, performed according to the technics previously described, led to the study of a new technical method, the principal characteristics of which consisted in blocking, by means of a definite point of deep osseous reference, i. e., the transverse process of the sixth cervical vertebra, the middle cervical and stellate ganglions without any of the accidents which have been indicated.

From an experimental study of the technics already known, I was convinced that accidents would occur whenever the needle touched the stellate ganglion directly, whether the anterior, the anterolateral, the external or the superoexternal approach was used.

This observation led me to study the topographic and anatomic relations of the stellate ganglion to the skeleton, to neighboring vessels, to the brachial plexus and to the pleura. From these investigations I deduced the possibility of obtaining, without accidents, block of the middle cervical, intermediate and stellate ganglions by means of descending infiltration anesthesia of these ganglions, with the needle inserted at the level of the base of the anterior surface of the transverse process of the sixth cervical vertebra. If, however, the anesthetic does not diffuse downward sufficiently to block completely the stellate ganglion, the needle must be inserted a second time and directed to the base of the transverse process of the seventh cervical vertebra, and the anesthetic must be injected close to the intermediate ganglion and the vertebral artery. In this manner, one can obtain a safe block of the middle cervical, intermediate and stellate ganglions.

Besides criticizing the several technics previously employed and describing the technic of stellate ganglion block with descending infiltration anesthesia, I have evaluated the signs which verify the physiologic interruption of the ganglions. The principal indications for employing either single or repeated blocks of the middle cervical and stellate ganglions as a diagnostic method, as a preoperative test for stellectomy or as a therapeutic method have been established.

Dr. A. Lamont, physician in charge of anesthesia at the Johns Hopkins Hospital, gave advice and encouragement in the preparation of this paper.

The Johns Hopkins Hospital, Baltimore.

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PROTEIN METABOLISM DURING CONVALESCENCE AFTER TRAUMA

RECENT STUDIES

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In the past several years many advances have been made in the field of protein metabolism. Under the stimulus of war especial interest has been directed toward protein metabolism after trauma of various sorts and during convalescence. The studies which will be summarized briefly here have, in the main, been carried out under the auspices of the Committee on Medical Research of the Office of Scientific Research and Development; many of them have been reported in an informal and preliminary manner at the Conferences on Metabolic Aspects of Convalescence, sponsored by the Josiah Macy Jr. Foundation.[1] At the outset it may be stated that the present state of knowledge leaves many problems yet unsolved, especially in regard to the mechanisms of the physiologic processes during periods of great wastage of nitrogen, when the organism consumes large portions of its vital tissue constituents in an effort to repair itself or to defend itself against injury.

The fundamental pattern of protein metabolism in healthy, vigorous persons subjected to injury may be illustrated by the chart of a patient recovering from fracture of the tibia (chart 1). On a well rounded diet, with approximately 120 Gm. of protein and 3,000 calories per day, this patient lost about 200 Gm. of body nitrogen during the first thirty days after his injury. The average loss of nitrogen in a group of cases of fracture, which my associates and I observed, was 225 Gm. In terms of protein this amounts to more than 1,400 Gm., and in terms of muscle protoplasm, approximately 15 pounds (7 Kg.). The average duration of the phase of negative nitrogen balance was thirty-five days. The maximal loss of nitrogen was not reached until six and six-tenths days (on the average) after the fracture occurred; the delay in reaching the peak of intensity was not due to slowed excretion of nitrogenous end products of protein catabolism, for the concentration of nonprotein nitrogen did not rise appreciably in the blood in this group of cases. After the nitrogen balance was reached (on an average of thirty-five days after fracture was sustained), recovery of lost nitrogen was slow; in the succeeding month or more the patients, lying in bed in casts, regained but a small

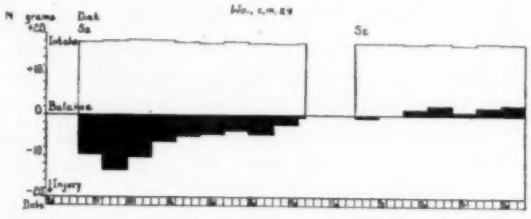

Chart illustrating the pattern of protein metabolism in a Negro woman aged 24 recovering from fracture of the femur (Howard, Parson, Stein, Eisenberg and Reidt [2]).

percentage of the nitrogen which they had lost during the phase of negative nitrogen balance.[2]

Operative cases (femoral osteotomy) were studied in a similar manner; the same pattern was shown qualitatively, but there was a much shorter phase of nitrogen loss (an average of only nine days); the losses of nitrogen were much smaller, averaging but 45 Gm., and in the subsequent periods these losses were rapidly restored.[2]

These movements of nitrogen after fracture and osteotomy confirm the observations of Cuthbertson, which are summarized in his Arris and Gale Lecture of 1942.[3] Similar observations were made on patients during convalescence after fractures by Browne, Stevenson and Schenker [1a]

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1. Minutes of the Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing, New York, Josiah Macy, Jr., Foundation: (*a*) Fifth Meeting, Oct. 8-9, 1943, p. 50; (*b*) Sixth Meeting, Feb. 11-12, 1944, p. 151; (*c*) p. 156; (*d*) p. 67; (*e*) Fifth Meeting, Oct. 8-9, 1943, p. 57; (*f*) Fourth Meeting, June 11-12, 1943, p. 113; (*g*) p. 22; (*h*) Seventh Meeting, June 9-10, 1944, pp. 117 and 120.

2. Howard, J. E.; Parson, W.; Eisenberg, H.; Stein, K. E., and Reidt, V.: Studies on Fracture Convalescence: I. Nitrogen Metabolism After Fracture and Skeletal Operations in Healthy Males, Bull. Johns Hopkins Hosp. **75**:156, 1944.

3. Cuthbertson, D. P.; Post-Shock Metabolic Response (Arris and Gale Lecture), Lancet **1**:433, 1942.

and by Albright and Reifenstein.[1b] Types of trauma other than fracture and osteotomy have produced this same general pattern of destruction of protein. It has been found in patients after burns by Browne;[1c] in patients with various types of infection, including meningitis and virus pneumonia, by Peters;[4] in patients with empyema and wounds of the chest by Browne,[1a] and in patients suffering from induced malaria by Howard and Bigham.[5]

The known facts regarding this fundamental pattern of increased destruction of protein may be summarized as follows:

1. The nitrogen deficit is brought about by increased excretion of nitrogen in the urine. It has repeatedly been shown that, unless complicating gastrointestinal lesions occur, there is no more than a normal amount of nitrogen in the stools; hence, the reaction does not involve an abnormality in the intestinal absorptive mechanism.[2]

2. Urinary nitrogen is mostly in the form of urea.[3] Normally, urea (urea plus ammonia) constitutes 80 to 90 per cent of the urinary nitrogen; in the reaction here under consideration, when as much as 40 or 50 Gm. of nitrogen was excreted per day in the urine, urea and ammonia accounted for 85 per cent or more of the nitrogen. Excretion of creatinine was unchanged, excretion of creatine was slightly increased in cases of fracture, as might be expected, and excretion of uric acid was only slightly greater than normal.[3] One might conclude from this observation that disposition of the nitrogenous portion of catabolized protein after trauma follows the same pattern as in health.

3. Fever per se will not account for the reaction. Many of our patients with fractures were free of fever. Patients with malaria excreted far more nitrogen than could be accounted for by a 7 per cent increase in total metabolism for each degree of elevation of temperature.[6] Furthermore, as will be evident later, certain patients may have fever of considerable magnitude and yet not exhibit any increase in protein metabolism. I do not mean to imply that infections and other conditions causing fever do not promote and exaggerate protein catabolism, for it is my co-workers' and my conviction that they do.[7]

4. Sulfonamide drugs had no effect per se on the reaction, either in altering the intensity of the protein catabolism or in bringing about any change in the absorption of foodstuffs.[2] My associates and I do not include in this category, of course, toxic reactions to the sulfonamide compounds, on which we have no data. Furthermore, it is our belief that, in their capacity to reduce the manifestations of infection, sulfonamide drugs would have the effect of reducing the intensity of protein catabolism.

5. Atrophy of disuse will account for only a small part of nitrogen loss.[8] Patients immobilized in casts after osteotomy were subjected to exactly the same "disuse" as were those with fracture; yet the quantitative aspects of the picture of protein metabolism were very different in the two groups.

6. Protein metabolism in healthy, vigorous patients after trauma differs from that during simple starvation. In starvation protein stores are called on presumably to furnish fuel and other metabolic needs of the organism. After a brief initial period of starvation, during which glycogen stores are utilized and but little nitrogen is lost, there is a steady loss of nitrogen, amounting to about 10 Gm. per day in an average-sized man.[9] This loss of nitrogen can be appreciably reduced by feeding carbohydrate, and quickly stopped by giving a diet which provides adequate calories and protein. But it has been found that in healthy persons after trauma high caloric diets, with large quantities of protein, often do not appreciably spare the body nitrogen at the height of a vigorous protein catabolism reaction whether the protein is administered orally, as highly nutritious food,[10] or intravenously, as amino acids.[1] There is certainly some nitrogen-sparing effect of such therapy during mild reactions and during the periods of waxing and waning of the vigorous reactions; yet the effect is strikingly different in degree from the reversal of loss of nitrogen obtained with similar therapy in cases

4. Peters, J. P.: Problems of Nitrogen Metabolism, Federation Proc. **3**:197, 1944.

5. Howard, J. E., and Bigham, R. S., Jr.: Unpublished data.

6. It might be argued that the destruction of red blood cells associated with malaria should be taken into account; on the other hand, the protein content of such cells should, under normal states, be available for reutilization and the over-all nitrogen balance thus be relatively unaffected (Robscheit-Robbins, F. S.; Miller, L. L., and Whipple, G. H.: Hemoglobin and Plasma Protein: Simultaneous Production During Continued Bleeding as Influenced by Amino Acids, Plasma Hemoglobin and Digests of Serum, Hemoglobin and Casein, J. Exper. Med. **77**:375, 1943).

7. Howard, J. E.; Winternitz, J.; Parson, W.; Bigham, R. S., Jr., and Eisenberg, H.: Studies on Fracture Convalescence: II. The Influence of Diet on Post-Traumatic Nitrogen Deficit Exhibited by Fracture Patients, Bull. Johns Hopkins Hosp. **75**:209, 1944.

8. Howard and others.[2] Cuthbertson.[3]

9. Benedict, F. G.: A Study of Prolonged Fasting, Publication 203, Carnegie Institute of Washington, 1915.

10. Howard and others.[2] Cuthbertson.[3] Peters.[4]

of simple starvation. Plasma protein, however, does seem to act as an efficient nitrogen-sparing agent [18] in cases so far studied, even with vigorous protein catabolism; this fact should be taken into account in any theoretic consideration of the mechanism of the reaction.

Another way in which the protein catabolism reaction after trauma differs from that due to starvation is in the behavior of potassium. In starvation, after the initial large output of potassium that presumably accompanies utilization of glycogen, the losses of nitrogen and potassium remain constant, at a ratio of approximately 10:1, which is the proportion in which these substances occur in muscle protoplasm.[11] However, during vigorous protein catabolism after fracture, when the patient is adequately fed, there has been observed no coincident loss of potassium, but often a positive potassium balance, even during the periods of greatest loss of nitrogen.[12]

7. All patients do not react alike to what is apparently the same stimulus. Considerable variation was observed in the magnitude of the loss of nitrogen in our studies on fracture. In an emaciated patient, the nitrogen balance was maintained even on a low intake of protein.[12] Peters likewise found that nitrogen equilibrium could be maintained in some patients suffering from acute infections with comparative ease, though most patients had large losses of nitrogen, which could not be prevented by feeding a diet high in protein.[4] Browne pointed out that after a long chronic illness it was a simple matter to maintain nitrogen equilibrium in a patient, even with continuing fever; in fact, strong positive nitrogen balances were effected in his chronically ill patients with high calories and protein.[16] Co Tui maintained nitrogen equilibrium, and even positive nitrogen balance in his patients with chronic gastric lesions after extensive surgical procedures.[16] The patients with malaria observed by Howard and Bigham seemingly responded to early chills with more vigorous protein catabolism than to later chills of apparently similar severity.[5] Cuthbertson found that rats previously starved of protein did not lose nitrogen after fracture while normally fed rats invariably did.[18] From these observations it must be concluded that the capacity to respond to trauma with increased breakdown of protein is a variable factor, being great in some subjects and reduced or practically absent in others.

11. Fenn, W. O.: Potassium in Physiological Processes, Physiol. Rev. **20**:377, 1940.

12. Howard, J. E.: Metabolic Observations on Patients Convalescent from Fractures, Tr. A. Am. Physicians, 1944, to be published.

COMMENT

These, then, are the main facts that have so far come to light in regard to the protein catabolism reaction after various sorts of injury. Though one is hardly in a position now to make any sweeping conclusions as to either the mechanism of the reaction or its therapeutic implications, it is perhaps desirable to reflect and make a few tentative deductions.

Judging from the magnitude of the nitrogen losses under consideration in this discussion, the main source of the lost nitrogen must be the body tissues—the protein of the cells. Some cells have doubtless furnished proportionately much more nitrogen and some much less than others. In all likelihood the same "available" nitrogen stores are called on and sacrificed in this reaction as were used to replenish plasma protein when this element was constantly removed from dogs in Whipple and Madden's classic experiment.[13]

It seems hardly worthy of argument that a person is better off before his nitrogen stores have been wasted than after. Surgeons have long noted that chronically debilitated patients are poor operative risks. Mulholland and associates reported that their patients whose stores of protein were depleted experienced quick healing of decubitus ulcers when they were given large amounts of amino acid.[14] Patients with burns respond much better to skin grafting after their nitrogen stores have been repleted.[15] The dogs used in Whipple and Madden's experiment which were depleted of protein were poorly resistant to all sorts of injurious agents, as compared with normal dogs.[13] In the case of susceptibility of liver to chloroform poisoning, the most important absent factor proved to be methionine, and replacement of this single element restored hepatic resistance to normal.[16] Time may reveal specific defects of this or other amino acids in other instances of increased susceptibility to toxic agents. It may be that in the protein catabolic response to injury the organism is really seeking an excess of one or more specific amino acids. Administration of amino acids,

13. Whipple, G. H., and Madden, S. C.: Hemoglobin, Plasma Protein and Cell Protein: Their Interchange and Construction in Emergencies, Medicine **23**:215, 1944.

14. Mulholland, J. H.; Co Tui; Wright, A. M.; Vinci, V., and Shafiroff, B.: Protein Metabolism and Bed Sores, Ann. Surg. **118**:1015, 1943.

15. Madden, S. C.: Personal communication to the author, to be published.

16. Miller, J. L., and Whipple, G. H.: Liver Injury, Liver Protection and Sulfur Metabolism, J. Exper. Med. **76**:421, 1942.

individually and in groups, and study of excretion of specific amino acids during the posttraumatic state (as is being carried out on normal persons by Holt and Albanese) may provide the answer to this question. At any rate, it seems justifiable to conclude for the present that, other things being equal, full nitrogen stores are a valuable asset to the resistance of the organism and that prevention of depletion of such stores and repletion of them if lost are worthy of therapeutic efforts.

It is clear also, from the foregoing comments, that the capacity to respond to injury with increased breakdown of protein is an asset to the organism. It is the healthy, vigorous, well fed patient who responds to a given injury with the greatest breakdown of protein. It does not necessarily follow that his wound will heal faster or resist infection better, for many other factors enter into recovery and return to fitness. Nevertheless, in the present state of knowledge, a wise patient should prefer to possess the capacity to respond with large losses of nitrogen. He should like, also, to have his cellular stores kept replete with nitrogenous components for maximal efficiency in whatever duties they might be called on to perform—provided that, in the keeping of them thus stored, no more important functional elements of the body are sacrificed.

Many more data are needed before categorical answers can be given to the questions of how much protein to administer, and when and how. When time is not at a premium, the refilling of protein stores should render the protein-depleted patient a better surgical risk. During convalescence repletion of lost protein should also improve his status. Since it is usually easiest to achieve a positive nitrogen balance in persons who have lost large amounts of body protein, administration to such patients of high protein diets before operation and as soon afterward as is practicable is clearly indicated. In instances in which, owing to a pathologic condition in the gastrointestinal tract or elsewhere, oral ingestion of a high protein diet is impossible, amino acids or plasma proteins may be administered by vein, with considerable benefit.

It was previously pointed out that in a vigorous reactor, at the height of an intense reaction, even large amounts of nitrogen, fed as protein food or given intravenously as amino acid, fail to spare to any appreciable degree the nitrogen waste. It has been my experience that healthy, vigorous patients rarely have much appetite at such a time and forced feeding, either by persuasion or by stomach tube, is utterly impractical, and usually impossible. Furthermore, forced peroral feeding to sick patients may well tend toward embarrassment of the circulation by promoting acute gastric dilatation. Forced oral feeding of these patients may thus be injurious, as well as fail to spare body protein. It would perhaps be wiser to give the bare maintenance protein and caloric requirements by intravenous administration of dextrose, amino acids and plasma and to feed higher protein diets later, after the greatest intensity of the protein catabolism has waned. In emergency operations on patients whose protein stores are depleted and to whom further losses of nitrogen would presumably be most harmful, mixtures of amino acids, given intravenously during the early periods after operation or injury, have proved most helpful.[1e] Fortunately, too, these patients are the ones in whom positive nitrogen balance is easily induced. During intravenous administration of a protein hydrolysate Howard and Bigham noted that the serum nonprotein nitrogen rose to 70 mg. or more per hundred cubic centimeters, presumably most of this nonprotein nitrogen being amino nitrogen, for the serum urea concentration remained normal.[5] No harmful effects were noted from the elevation of nonprotein nitrogen, and there was a rapid fall to normal with cessation of the therapy.

Concerning the fundamental nature and mechanism of the protein catabolism reaction there is as yet no knowledge. From the types of situations in which the reaction has been found, one is tempted to guess that the stimulus to its production is probably in some way associated with the absorption of the products of devitalized tissue. The capacity to respond to the stimulus seems closely associated with the amount and availability of body protein. However, that it is simply a matter of the degree of fulness of the warehouses of protein is unlikely. There may be required an intermediary factor, such as a principle of the adrenal or the pituitary gland, as suggested by Albright and Browne.[1g] Indeed, Venning found increased quantities in the urine of a substance capable of promoting gluconeogenesis in adrenalectomized rats during convalescence from injury.[1h] It is my impression, derived from observations in this group of cases, that administration of large quantities of protein is the most effective way so far found of prolonging the protein catabolism reaction; conversely, undernutrition is the most effective way of shortening it. These observations may be important when it is learned whether a large protein turnover is helpful or harmful to rapid repair and convalescence in general.

Finally, of course, many factors other than protein metabolism are of greatest importance in the over-all picture of convalescence. The cir-

culation, the fluids of the extracellular compartment in which the cells are bathed and many other physiologic factors, including availability of necessary vitamins, must be in the most desirable state for the cells to function at their maximal efficiency.

SUMMARY AND CONCLUSIONS

Traumas of a wide variety increase protein metabolism. In reactions of great magnitude there may be extensive wastage of nitrogen and great losses of body protein. The vigor of the protein catabolism depends on two factors: (1) the intensity of the stimulus and (2) the capacity of the organism to respond to the stimulus. The stimulus may be related to the absorption of devitalized tissues; the capacity to respond appears, to some degree at least, to be related to the previous state of protein nutrition.

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USE OF OMENTUM TO CLOSE PERFORATIONS OF THE STOMACH

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It is common practice to cover perforated ulcers of the stomach with tabs of omentum, especially when the adjacent gastric wall is too indurated and friable for satisfactory closure of the hole with sutures alone. Free omental transplants, or grafts, have been recommended for that purpose, and illustrations of such an operation may be found in current surgical textbooks.

On theoretic grounds it may be questioned whether this procedure is sound surgical practice. One might expect the free transplants, deprived temporarily of a blood supply, to be susceptible both to the digestive action of gastric juice and to infection, which is sure to be present, at least part of the time. In that case the safer procedure would be to cover the defects only with living omentum, which presumably would offer greater resistance to both digestion and infection.

EXPERIMENTAL PROCEDURE

We have studied this problem experimentally by means of operations on dogs.

Healthy stock animals were used. With the dogs under light anesthesia induced with pentobarbital sodium, and with aseptic technic, round or oval holes were cut in the anterior gastric wall. These artificial perforations were then covered with omentum in various ways. The holes were deliberately made larger than the perforations encountered clinically because we wished to subject the covering omentum to relatively severe tests, and also because small holes in the normal gastric wall heal too rapidly to present the problems posed by the more slowly healing perforations of peptic ulcer. Cotton thread was used for sutures and ligatures. All the animals were allowed water and food (dog pellets) ad libitum after operation. Surviving animals were subjected to exploratory operation or were killed after various intervals, in order to study the process of repair.

PROTOCOLS

The experiments performed and the results observed are indicated in the following protocols:

A. Hole Covered with Living Omental Patch.—1. A large hole, 3 by 4.5 cm., was cut in the anterior gastric wall. After bleeding had been stopped, the hole was covered with a double thickness of omentum. Interrupted sutures around the margins anchored the patch in place. This omentum, as is so often the condition in dogs, was poor in fat and in places appeared extremely thin and delicate. Peritonitis did not develop, but the animal seemed unwell and lost considerable weight. After twenty-one days the dog was killed. The patch, now thick and fibrosed, was tightly adherent to the site of the stoma. From the gastric side the hole appeared as a shallow crater, 1 by 1 cm. Microscopic sections showed sluggish proliferation of gastric epithelium, extensive and dense fibrosis of the omental patch and, at the surface of the crater, a layer of hyalinization, necrosis and sloughing.

2. An even larger hole, 3 by 6 cm., was made in the anterior gastric wall. A sample of fasting gastric contents taken at this time showed 23.4 units of free acid and 34 units of total acid. The hole was covered with a double layer of omentum, as just described. Peritonitis did not occur; the dog remained healthy and gained weight. The animal was killed after one hundred and five days. The omental patch appeared densely fibrosed and adherent. The gastric defect had almost healed, a small crater remaining. Histologic examination revealed superficial inflammatory reaction, necrosis and sloughing of the surface of the crater and dense fibrosis of the underlying omentum, extending to a depth of about 1 cm., at which level normal fat was encountered.

B. Hole Covered with Free Omental Patch.—1. A hole, 1.5 by 2 cm., was covered in the manner previously described with a double layer of omentum, but the patch was then cut free from the parent omentum. Gastric contents contained 30 units of free acid and 42.5 units of total acid. The animal died within twenty-four hours with general peritonitis. Necropsy showed that the patch was entirely necrotic and leaked like a sieve.

2. Method 1 was repeated. The hole was 1.5 by 1.5 cm. The dog used in this experiment likewise died within twenty-four hours with general peritonitis. The patch was necrotic, with multiple perforations.

3. A hole, 2 by 2 cm., was covered as before with a free patch of omentum. This patch also became necrotic, and the dog died with peritonitis.

C. Hole Stopped with Living Tab of Omentum.—1. A hole, 1 by 1 cm., was cut. A tongue of omentum was drawn up over the defect and was fastened lightly in place with overlying mattress sutures. Exploration after twenty-four hours showed that there had been no leakage. Grossly the omentum adherent to the hole appeared normal, but microscopically there was a superficial inflammatory reaction where the plug had been exposed to the action of gastric juice.

2. A hole, 1 by 1.5 cm., was similarly covered with a tongue of living omentum. The dog, which remained well, was killed after eight days. The omental plug was tightly adherent and fibrosed. There had been no leakage. Microscopic examination showed beginning proliferation of gastric epithelium at the margins of the crater, with acute inflammatory reaction and fibrosis of the plug generally. Near the surface of the crater

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there were hyalinization and sloughing of necrotic material into the lumen of the stomach.

3. A hole, 0.5 by 1 cm., was covered as before with a tab of living omentum. The dog remained healthy and was killed after sixty-one days. Gross and microscopic examination revealed a fibrosed tab of omentum, but the gastric defect had healed, with complete epithelization.

4. A hole, 2.5 by 3 cm., was covered with a tongue of living omentum. The dog remained vigorous and healthy. After fifty-seven days exploratory operation revealed a living, fibrosed, adherent plug, completely covered with regenerated tissue of the gastric wall.

D. Hole Stopped with Free Tab of Omentum.—1. A hole, 2 by 2 cm., was covered in the manner just described with a tongue of omentum, which was fastened with five looping mattress sutures. The parent omentum was cut free. General peritonitis developed, and the dog died in less than twenty-four hours. The plug was necrotic, permitting leakage of gastric contents. The adjacent gastric mucosa had an irregular zone of necrosis, and at one place the gastric wall had perforated spontaneously.

2. A transverse ellipse, 3.5 cm. long, was covered with a free tongue of omentum. Local, then general, peritonitis developed, and the dog died twelve days after operation. The plug was entirely necrotic. Extensive adhesions represented unsuccessful efforts of the parent omentum and the intestine to wall off the infection. The gastric defect showed no evidence of healing.

3. A hole, 1.5 by 1.5 cm., was stopped with a free tab of omentum. The animal survived and was killed after eight days. Grossly the omental tab appeared necrotic, perforation and peritonitis having been averted by the parent omentum, which overlay the plug and was tightly adherent to the stomach. Microscopically there were active proliferation of the marginal gastric epithelium, necrosis and multiple abscesses throughout the plug and an inflammatory reaction, with fibrosis, in the adjacent parent omentum.

4. An oval hole, 0.5 by 1 cm., was covered with a free tab of omentum. The dog, which remained healthy, was killed after sixty-one days. Both grossly and histologically the plug showed multiple abscesses and necrosis, perforation having been averted by the protective action of the adherent parent omentum. The gastric stoma had nearly healed, however, by fibrous constriction and epithelial proliferation.

5. A hole, 3 by 3.5 cm., was covered as before with a free omental graft. The dog remained healthy and was examined after fifty-seven days. The omental plug was densely fibrosed but was living. The gastric defect had partly healed. Microscopic section showed that the plug was receiving a rich new blood supply from the parent omentum, which overlay it.

6. Two oval openings in the anterior gastric wall were each covered with a free tab of omentum; the parent omentum was then excised, so as to eliminate the protective action demonstrated in the preceding 5 experiments. The dog remained well and was killed after fifteen days. Both tabs were fibrotic and contained numerous microscopic abscesses. The gastrosplenic ligament had come up to cover the grafts, thus averting probable perforation and peritonitis.

E. Unsutured Gastric Incision Covered with Free Omental Graft.—1. A transverse incision in the anterior gastric wall was not sutured, but it was covered with a free omental graft, which was fastened lightly in place with over-arching sutures. The dog, which remained healthy, was killed after twenty-one days. The adherent omental tab was somewhat fibrosed but living; it contained no abscesses. It was not adherent to the parent omentum or to any surrounding structures; its new blood supply apparently came entirely from the gastric wall. The gastric incision was shown by microscopic section to have healed completely, with minimal inflammatory reaction.

2. Procedure 1 was repeated. A transverse incision, 2 cm. long, unsutured, was covered with a free tab of omentum. Analysis of the gastric contents (fasting) showed 37.1 units of free acid and 67.2 units of total acid. The animal remained healthy and was subjected to exploratory operation after ten days. The site of the graft was adherent to the liver and the anterior abdominal wall. The graft itself was indurated and inflamed. The gastric incision appeared healed.

Résumé of Experimental Results.—A. Large Hole Covered with Living Omental Patches: For this experiment 2 dogs were used; both survived. The gastric defects healed slowly over the patches, which were greatly thickened and fibrosed but which showed only superficial necrosis and sloughing at the gastric surface.

B. Smaller Holes Covered with Free Omental Patch: Three dogs were used for this experiment; all died with general peritonitis. All the grafts were necrotic, with multiple perforations.

C. Hole Stopped with Tab of Living Omentum: None of the 4 dogs used for this experiment died. All the plugs showed fibrosis, acute inflammatory reaction and superficial necrosis where they were exposed to the action of gastric juice.

D. Hole Stopped with Free Tab of Omentum: Six dogs were used for this experiment; 2 died with general peritonitis from necrosis and perforation of the grafts; in 3 of the 4 surviving animals the plugs were largely necrotic, and perforation and peritonitis probably had been averted only by the protective action of the parent omentum and adjacent structures in sealing off the grafted area. Only one of the seven grafts lived and proved to be an effective seal; this graft had received a rich blood supply from the parent omentum.

E. Unsutured Gastric Incision Covered with Free Omental Graft: Both dogs subjected to this procedure survived. The grafts showed inflammatory reaction but lived, owing to adequate circulation from adjacent tissues. The incisions had healed promptly.

COMMENT

It is clear from these experiments that living patches or tabs of omentum may be used safely to cover defects, and even large holes in stomachs of dogs. These seals become fibrotic, but they resist infection and digestion and do not tend to leak. Free omental transplants, on the contrary, are liable to infection, necrosis and digestion; they tend to perforate, with resultant leakage and

peritonitis. In several instances peritonitis was averted by the protective action of the parent omentum, but in such cases it would be more sensible and safer simply to seal the holes with living omentum at operation.

Although these experiments on healthy canine stomachs do not reproduce exactly the situation in perforated gastric ulcers, they do suggest that living omental or mesenteric tabs can be used to cover these defects with less risk than is involved with free transplants of omentum.

SUMMARY

Living omental patches or tabs were used successfully to cover relatively large holes in the stomachs of dogs. Such seals appeared to be highly resistant to digestion and infection, giving the gastric defects time to heal.

Free omental transplants similarly employed, being temporarily without any blood supply, are susceptible to infection and the corrosive action of gastric juice. Necrosis and perforation of the graft occurred in many instances.

These experimental results suggest that in clinical surgical procedures it is more rational and safer to use living tissue than free omental grafts to cover perforated gastric ulcers or to reenforce lines of anastomosis.

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CYSTS OF THE URACHUS

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The allantois is a fetal membrane which develops from the hindgut. Externally it helps to form the placenta and umbilical cord, and internally the urinary bladder develops as a dilatation of its distal end.

The intra-abdominal portion of the allantois, between the umbilicus and the bladder, is the urachus. In normal development this remains as the middle umbilical ligament, which is a cord passing from the apex of the bladder along the posterior surface of the anterior abdominal wall to the umbilicus.

In a small number of cases the obliteration of this canal is not completed at birth, and several types of anomaly may result. The condition has been discovered twice as often in males as in females. It is probably most frequently found in infants at birth or after separation of the umbilical stump. It may first manifest itself in the baby as some form of irritation about the navel. This has been called the congenital type, as opposed to the so-called acquired type, discovered later in life. This distinction, however, like the use of the same terminology in classifying inguinal hernias, is misleading. All pathologic conditions of the urachus are basically congenital. No doubt there are many instances of patent urachus which, because of lack of symptoms, are never discovered.

Vaughan [1] classified the types of patent urachus as follows: (1) the canal which is open all the way from the umbilicus to the bladder; (2) the duct which is closed at the bladder but open at the umbilicus; (3) the urachus which is closed at the umbilicus but opens into the bladder; (4) the "blind" type, in which both the umbilical and the vesical end are closed but some intervening part or parts of the duct remain open.

Types 1 and 2 account for the formation of fistulas, although because of infection the other types may form fistulas also. The "blind" type is responsible for the development of urachal cysts. Colston [2] stated that the secretory activity of the epithelial membrane which lines the pocket or canal may produce a cyst at any age. Even if not primarily infected, such an accumulation is prone to become so, and many things may happen. Desquamated epithelial debris may partially or completely block the canal. The epithelial lining of the canal or of a subsequent cyst may be more or less completely destroyed by persistent infection. At the same time the fibrous tissue wall of the canal or the cyst will be greatly increased by the same process. Most of these cysts are small and confined to the anterior abdominal wall at or near the midline. Their clinical course has been compared with that produced by a pilonidal cyst.

Through chronic exudation and retention over a considerable period, some of these cysts may increase greatly in size and invade the abdominal cavity. Some will be the size of an orange or grapefruit, but several cases have been reported in which a mistaken diagnosis of ovarian cyst, ascites or even pregnancy has been made. Peritonitis due to rupture of a large urachal cyst has been described, and there are reports of formation of fistulous tracts with ovarian and dermoid cysts. The development of a malignant growth, which is likely to involve the bladder early, has been mentioned in the literature several times. This complication may come with either a small or a large cyst.

The distortion produced by a large cyst of the urachus may make an accurate diagnosis as to its origin difficult. This is especially true if there is an entire absence of suggestive history. In the reports on large cysts there is little or no evidence of previous symptoms pertaining to the bladder. The topographic relationships of a large urachal cyst and its location and point of attachment to the apex of the bladder, which are revealed at operation, must be relied on in making the diagnosis. If the epithelial lining has been destroyed, there will be no distinctive or characteristic features of the wall of the cyst, either macroscopic or microscopic, which will verify its origin.

REPORT OF A CASE

C. E. M., a white man aged 64, a railroad official, married, with two grown sons, entered the hospital

1. Vaughan, G. T.: Patent Urachus, Tr. Am. S. A. **23**:273-294, 1905.

2. Colston, J. A. C.: The Urachus, in Nelson Loose-Leaf Living Surgery, New York, Thos. Nelson & Sons, 1928, vol. 6, chap. 6, p. 373.

on Nov. 10, 1942 for examination. At irregular intervals for several years he had had attacks initiated by a slight chill, followed by fever and general malaise. The attacks were sometimes, but not always, associated with intestinal disturbance. There was some abdominal soreness but not much pain. The attacks were unrelieved by bowel movements and lasted one or two days. In the last year there had been increasing abdominal distress, which was not always associated with these attacks. The distress seemed to be intestinal rather than gastric, but it had no particular pattern. Frequently it did not seem influenced by the type of food eaten. There were distention and soreness in the lower portion of the abdomen. The history suggested a spastic colon but was not always consistent with the usual findings. He was not constipated, and no blood had been noted in the stools. He had lost over 15 pounds (6.8 Kg.) in the last year, with a decrease in strength and general well-being.

He was a well built man, being over 6 feet (180 cm.) in height and normally weighing about 200 pounds (91 Kg.). Examination of the abdomen showed some general distention and a slightly movable mass to the left of the midline in the left lower quadrant. There was little local tenderness. Proctoscopic examination gave no evidence of a pathologic process. Fluoroscopic

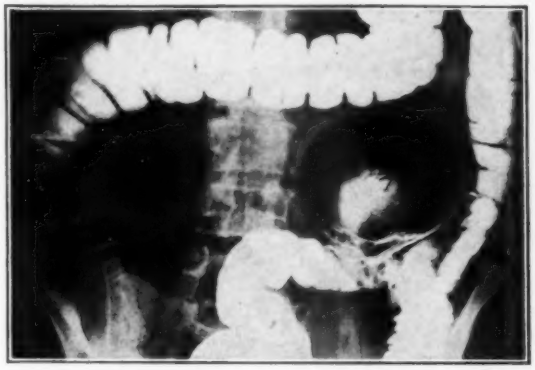

Fig. 1.—Roentgenogram (Nov. 11, 1942) showing the colon filled with barium sulfate, some of which has passed through the fistula into the cyst.

examination, made immediately after administration of an enema of barium sulfate, revealed marked spasm in the lower portion of the colon; but after five minutes the entire colon filled to its capacity, and on the median side of the sigmoid small quantities of the emulsion entered a diverticulum the size of a grapefruit. Roentgenograms made after evacuation revealed some retention of barium in the colon and in the diverticulum. They further showed several small diverticula of the sigmoid. Roentgenograms taken twenty-four hours later showed the large diverticulum in both anteroposterior and lateral projections. They revealed it to be nearly empty and in a position adjacent to the anterior abdominal wall. The Kahn reaction of the blood was negative. There were 3,800,000 red blood cells, 10,000 white cells and a hemoglobin content of 78 per cent. The urine and the stools were normal.

Operation was advised but not submitted to at this time. The patient was placed on a careful bland diet and observed frequently. For the following nine months he continued to function at his office about half the time but was never well, and all previous symptoms became slightly aggravated.

He reentered the hospital on Aug. 17, 1943, and roentgenographic and other check-up examinations were repeated, with similar results. He had lost 15 more pounds (6.8 Kg.), and the diverticulum seemed slightly larger. At operation, on August 21, an incision 7 inches (18 cm.) in length was made slightly to the left of the tumor mass. The presenting cystic tumor was somewhat movable laterally but not in a superior-inferior direction. It was lying just beneath the anterior abdominal wall, with the cystic, or larger, part of the mass in a superior position, while medially and inferiorly it was continued as one structure, tapering down to a firm ropelike pedicle, 4 cm. in diameter. This became somewhat flattened and fanned out below to be firmly attached to the apex of the bladder and the anterior abdominal wall. The cystic mass was roughly spherical, with diameters varying from 10 to 14 cm. Approximately three fourths of the entire outer surface was free and smooth, with a normal-appearing peritoneal covering. A considerable area of the left lateral and posterior surface of the cyst was closely adherent to the sigmoid. This was dissected free to the point where a fistulous tract existed between the inside of the cyst and the lumen of the sigmoid. The

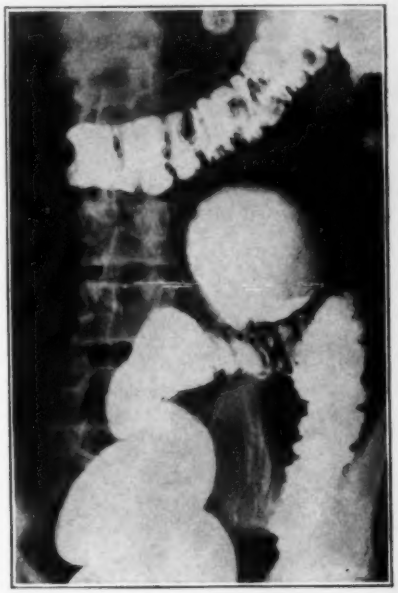

Fig. 2.—Roentgenogram (Aug. 18, 1943) showing a somewhat larger cyst and the passage of more barium through the fistula.

fistula was doubly clamped and severed, and the side next the sigmoid was satisfactorily repaired. The fistulous opening into the cyst was several centimeters distant from the solid, or pedicle, portion of the mass. Severing this firm structure allowed the removal of the cyst. It did not seem to contain a channel or canal, and, although there was a definite blood supply, the pedicle was for the most part like the wall of the cyst itself, densely fibrous. Sulfathiazole was sprinkled into the field and a Penrose drain inserted before closure.

The patient made an excellent recovery, without infection or other major complications. He had a good bowel movement on the sixth day postoperatively and fairly regular movements thereafter. He left the hospital on September 9 and continued to improve. He has had no serious symptoms since and has completely regained his weight, strength and general health.

The contents of the cyst consisted of fairly fluid, pale brownish red, foul-smelling material. The interior was lined by pale reddish gray to light brownish or grayish

tan tissue, which was extensively mottled with darker red. This lining measured up to 2 mm. in thickness and in areas had a coarsely mamillated appearance. The remainder of the wall of the cyst consisted of fairly dense, firm, grayish white fibrous tissue, measuring up to 0.7 cm. in width in areas. Microscopic examination revealed that dense fibrous tissue presenting pronounced chronic inflammation constituted the wall of the cyst. The interior was lined by granulation tissue with chronic inflammation. At the site of its detachment from the colon only was there noted a mucus-secreting colonic type of mucosa.

COMMENT

This cyst was believed to have been urachal in origin because of its anatomic relations. Its connection with the colon was thought to be incidental. The adjacent colonic wall showed in the roentgenogram small diverticula of the usual type; one may surmise that a perforation had occurred from the presence of one adjacent to the wall of the cyst, with resulting local peritonitis and eventual formation of the fistula. It is thought that a cyst or a diverticulum, either congenital or acquired, originating from the colon would have produced a more abrupt clinical episode in its incipiency, would have been found at operation to have less free, nonadherent surface and would have shown some gross or microscopic indications of its origin. It was evident that the large thick pedicle of this cyst contained an adequate blood supply for survival of the cyst, while the fistulous tract and adjacent adhesions lacked sufficient vascularity for survival of so large a mass.

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